NOMENCLATURE

Preparations appear in the alphabetical order of common names of the compounds. For convenience in surveying the literature concerning any preparation through *Chemical Abstracts* subject indexes, the *Chemical Abstracts* indexing name for each compound is given as a subtitle if it differs from the common name used as the title.

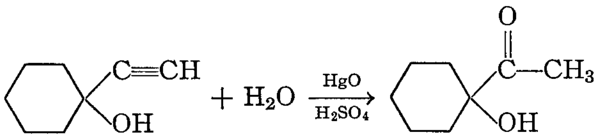
SUBMISSION OF PREPARATIONS

Chemists are invited to submit for publication in *Organic Syntheses* procedures for the preparation of compounds which are of general interest or which illustrate useful synthetic methods. The procedures submitted should represent, as nearly as possible, optimum conditions for the preparations, and should have been checked carefully by the submitter. Full details of all steps in the procedure should be included, and the range of yields should be reported rather than the maximum yield obtainable. The melting point of each solid product should be given, and the boiling-point range and refractive index (at 25°) of each liquid product. The method of preparation or source of the reactants and the criteria for the purity of the products should be stated.

Procedures submitted should be written in the style employed in the latest volume of *Organic Syntheses*. Copies of the current style sheet may be obtained upon request from the Secretary of the Editorial Board. Two copies of procedures which are submitted should be sent to the Secretary. Additions, corrections, and improvements to preparations previously published are welcomed and should be sent to the Secretary.

1-ACETYLCYCLOHEXANOL

(Ketone, 1-hydroxycyclohexyl methyl)



Submitted by Gardner W. Stacy and Richard A. Mikulec.[1]
Checked by John C. Sheehan, George A. Mortimer, and Norman A. Nelson.

1. Procedure

In a 1-l. three-necked round-bottomed flask, equipped with a sealed stirrer, a reflux condenser, a thermometer, and a dropping funnel, is dissolved 5 g. of mercuric oxide (Note 1) in a solution of 8 ml. of concentrated sulfuric acid and 190 ml. of water. The solution is warmed to 60°, and 49.7 g. (0.40 mole) of 1-ethynylcyclohexanol (Note 2) is added dropwise over a period of 1.5 hours. After the addition has been completed, the reaction mixture is stirred at 60° for an additional 10 minutes and allowed to cool. The green organic layer which settles is taken up in 150 ml. of ether, and the aqueous layer is extracted with four 50-ml. portions of ether (Note 3). The combined ethereal extracts are washed with 100 ml. of saturated sodium chloride solution (Note 4) and dried over anhydrous sodium sulfate. The drying agent is removed, the ether is evaporated, and the residue is distilled under reduced pressure through a 15-cm. column packed with glass helices. The 1-acetylcyclohexanol is collected at 92–94°/15 mm. as a colorless liquid, n_D^{25} 1.4670, d_4^{25} 1.0248 (Note 5). The yield is 37–38 g. (65–67%).

2. Notes

1. Mallinckrodt mercuric oxide red (analytical reagent or N.F. 1x grade) was used.

2. 1-Ethynylcyclohexanol is available from Air Reduction Chemical Company, 60 East 42 Street, New York 17, New York, or from Farchan Research Laboratories, Cleveland, Ohio. It can also be prepared as reported by Saunders.[2]

3. To facilitate subsequent extractions, the solid material remaining after separation of as much of the aqueous phase as possible should be removed by gentle suction filtration and washed with 25 ml. of ether.

4. The sodium chloride solution removes the green color from the ether extract, leaving a yellow solution.

5. The checkers found b.p. 100°/21 mm., n_D^{25} 1.4662–1.4665, d_4^{25} 1.0235–1.0238. Others have reported b.p. 92–94°/12 mm., d_0^{20} 1.0256;[3] b.p. 91°/11 mm., n_D^{11} 1.4726, d_4^{11} 1.1033;[4] b.p. 88.0–88.6°/12 mm., n_D^{28} 1.4712.[5]

Establishing a criterion for the purity of the product is of particular importance because of the known tendency of ethynylcarbinols to undergo rearrangement.[5,6] The authors have reported that consecutive small fractions of the distillate possess a constant boiling point and refractive index. Further, representative fractions, treated with periodic acid and subsequently with 2,4-dinitrophenylhydrazine, give cyclohexanone 2,4-dinitrophenylhydrazone in 83% over-all yield in a high state of purity.

3. Methods of Preparation

1-Acetylcyclohexanol has been prepared by the hydrolysis of 1-bromo-1-acetylcyclohexane[3] and of 1-acetoxy-1-acetylcyclohexane oxime,[7] by the hydration of 1-ethynylcyclohexanol,[4,5,8,9] and by the treatment of 1-hydroxycyclohexanecarboxylic acid with methyllithium.[10] The present procedure is based on that of Stacy and Mikulec for 1-acetylcyclopentanol.[6]

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[1] State College of Washington, Pullman, Washington.

[2] *Org. Syntheses* Coll. Vol. **3**, 416 (1955).

[3] Favorskii, *J. Russ. Phys. Chem. Soc.*, **44**, 1339 (1912) [*C. A.*, **7**, 984 (1913)].

[4] Locquin and Wouseng, *Compt. rend.*, **176**, 516 (1923).

[5] Newman, *J. Am. Chem. Soc.*, **75**, 4740 (1953).

[6] Stacy and Mikulec, *J. Am. Chem. Soc.*, **76**, 524 (1954).

[7] Wallach, *Ann.*, **389**, 191 (1912).

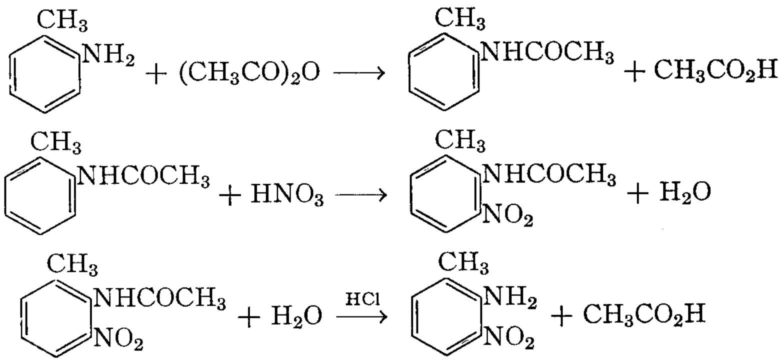
[8] Bergmann, Brit. pat. 640,477 [*C. A.*, **45**, 1622 (1951)]; U. S. pat. 2,560,921 [*C. A.*, **46**, 3072 (1952)].

[9] Stacy and Hainley, *J. Am. Chem. Soc.*, **73**, 5911 (1951).

[10] Billimoria and Maclagen, *Nature*, **167**, 81 (1951); *J. Chem. Soc.*, **1951**, 3067.

2-AMINO-3-NITROTOLUENE

(*o*-Toluidine, 6-nitro-)



Submitted by John C. Howard.[1]
Checked by Charles C. Price and Joseph D. Berman.

1. Procedure

A 1-l. three-necked flask is fitted with a sealed Hershberg stirrer, a reflux condenser, and a dropping funnel. The flask is charged with 650 ml. of acetic anhydride, and 107 g. (107 ml., 1 mole) of *o*-toluidine (Note 1) is introduced from the dropping funnel. The mixture becomes very warm. After the amine has been completely added, the solution is cooled to 12–13° in an ice-salt bath (Note 2). During the cooling, the dropping funnel and condenser are replaced by another dropping funnel containing 126 ml. (2 moles) of 70% nitric acid and a thermometer which can be read to within 0.5° in the range from 10° to 20° (Note 3).

The nitric acid is added drop by drop to the cold slurry at a rate which maintains the temperature carefully within the limits of

10–12° (Note 4). If the temperature persists in dropping, the addition is stopped after about 5 minutes. The ice bath is removed until the temperature rises 0.5°, the ice-salt bath is replaced, and addition is continued. As the reaction progresses, the acetotoluide which may have precipitated redissolves, and the solution becomes deeply colored. The addition is complete in 1–2 hours, and the nitro compounds may start to separate.

The solution is poured, with stirring, into 3 l. of ice water. The mixture of 4- and 6-nitroacetotoluides precipitates as a cream-colored solid which is collected on a large Büchner funnel. After thorough washing with four 500-ml. portions of ice water, the precipitate is partly dried by suction (Note 5). The moist product is then placed in a steam-distillation apparatus (Note 6), covered with 300 ml. of concentrated hydrochloric acid, and heated until the mixture boils. The acetotoluides are rapidly hydrolyzed, and the solution becomes dark red. Steam is then introduced, and the distillation is thus continued until 36 l. of distillate has been collected (Note 7). The 2-amino-3-nitrotoluene, which separates as bright orange needles when the distillate is cooled, is collected on a large Büchner funnel. The dried product amounts to 75–84 g. (49–55%), m.p. 92–94°. The product may be further purified by a second steam distillation. Ten grams of the amine is distilled from 150 ml. of water, and 3 l. of distillate is collected, yielding 8.7 g. of 2-amino-3-nitrotoluene, m.p. 95–96° (cor.).

2. Notes

1. Commercially available *o*-toluidine, b.p. 75–77°/10 mm., is suitable. Redistillation of this material gave no significantly better results. The checkers obtained a 42% yield of 2-amino-3-nitrotoluene using practical *o*-toluidine directly, and a 57% yield after redistillation.

2. The flask should be immersed up to the neck in the slurry of ice and salt. During the cooling, the acetotoluide may suddenly precipitate, immobilizing the stirrer; a few turns manually breaks up the mass of crystals and allows the stirring to be continued.

3. A low-temperature thermometer with a range from −15° to +50° is suitable.

4. If the temperature is allowed to rise above 18°, violent if not explosive decomposition may ensue.

5. The precipitate can be air-dried to a constant weight of 150–160 g.

6. An efficient steam-distillation apparatus such as that described by Fieser [2] is recommended. A 12-l. round-bottomed flask cooled in a tub of ice serves as the receiver, which is equipped with an auxiliary vertical condenser attached to a gas absorption trap [3] to accommodate the hydrogen chloride which distils first.

7. The third 12-l. portion yields about 20 g. of 2-amino-3-nitrotoluene. The residue in the steam-distillation flask, about 20 g. of crude 2-amino-5-nitrotoluene, solidifies when cooled and may be separated by filtration. It can be recrystallized from 2 l. of hot water, yielding 14–15 g. of yellow plates, m.p. 130–131° (cor.).

3. Methods of Preparation

2-Amino-3-nitrotoluene has been prepared by the nitration of oxalotoluide [4] and by the nitration of *o*-acetotoluide in acetic acid with fuming nitric acid [5] or with a mixture of nitric and sulfuric acid.[6]

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[1] Cornell University, Ithaca, New York.

[2] Fieser, *Experiments in Organic Chemistry*, 2nd ed., p. 159 (Fig. 15), and p. 160 (Fig. 16), D. C. Heath and Company, Boston, Massachusetts, 1941.

[3] *Org. Syntheses* Coll. Vol. **2**, 4 (1943).

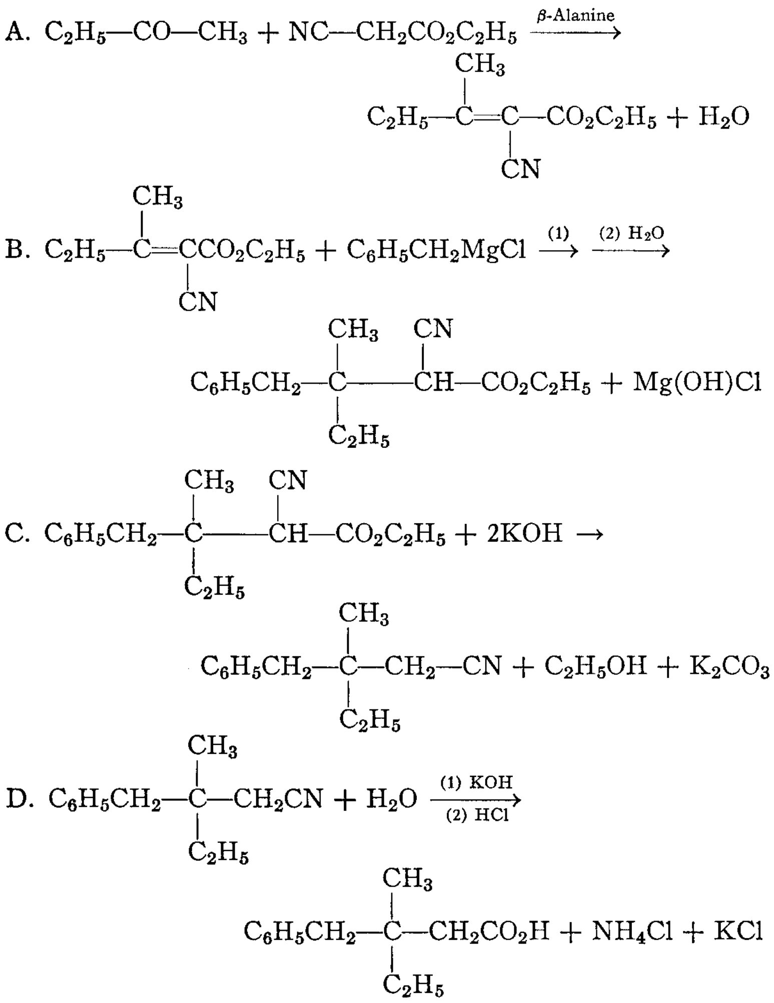
[4] Hadfield and Kenner, *Proc. Chem. Soc.*, **30**, 253 (1914).

[5] Cohen and Dakin, *J. Chem. Soc.*, **79**, 1127 (1901).

[6] McGookin and Swift, *J. Soc. Chem. Ind.*, **58**, 152 (1939).

3-BENZYL-3-METHYLPENTANOIC ACID

(β-Benzyl-β-methylvaleric acid)



A. $C_2H_5—CO—CH_3 + NC—CH_2CO_2C_2H_5 \xrightarrow{\beta\text{-Alanine}} C_2H_5—\overset{CH_3}{\overset{|}{C}}=\underset{\underset{CN}{|}}{C}—CO_2C_2H_5 + H_2O$

B. $C_2H_5—\overset{CH_3}{\overset{|}{\underset{\underset{CN}{|}}{C}}}=CCO_2C_2H_5 + C_6H_5CH_2MgCl \xrightarrow{(1)} \xrightarrow{(2)\ H_2O} C_6H_5CH_2—\overset{CH_3}{\overset{|}{\underset{\underset{C_2H_5}{|}}{C}}}——\overset{CN}{\overset{|}{C}}H—CO_2C_2H_5 + Mg(OH)Cl$

C. $C_6H_5CH_2—\overset{CH_3}{\overset{|}{\underset{\underset{C_2H_5}{|}}{C}}}——\overset{CN}{\overset{|}{C}}H—CO_2C_2H_5 + 2KOH \rightarrow C_6H_5CH_2—\overset{CH_3}{\overset{|}{\underset{\underset{C_2H_5}{|}}{C}}}—CH_2—CN + C_2H_5OH + K_2CO_3$

D. $C_6H_5CH_2—\overset{CH_3}{\overset{|}{\underset{\underset{C_2H_5}{|}}{C}}}—CH_2CN + H_2O \xrightarrow[(2)\ HCl]{(1)\ KOH} C_6H_5CH_2—\overset{CH_3}{\overset{|}{\underset{\underset{C_2H_5}{|}}{C}}}—CH_2CO_2H + NH_4Cl + KCl$

Submitted by F. S. PROUT, R. J. HARTMAN, E. P.-Y. HUANG, C. J. KORPICS, and G. R. TICHELAAR.[1]
Checked by JAMES CASON, K. C. DEWHIRST, E. J. GAUGLITZ, JR., and WILLIAM G. DAUBEN.

1. Procedure

A. *Ethyl sec-butylidenecyanoacetate.* In a 1-l. round-bottomed flask fitted with a 24/40 joint are placed 0.45 g. of β-alanine, 113 g. (106 ml., 1.0 mole) of ethyl cyanoacetate (Note 1), 87 g. (108 ml., 1.2 moles) of butanone, 20 ml. of glacial acetic acid, and 100 ml. of benzene. A Barrett-type water separator (Note 2) and a condenser are attached to the flask, and the mixture is heated briskly under reflux until water ceases to be collected in the trap (7–12 hours).

The reaction mixture is decanted into a 500-ml. round-bottomed flask which is attached to a fractionating column (Note 3). The solvent is removed at atmospheric pressure while the oil bath is heated finally at 160°. The residue is distilled at reduced pressure to furnish four fractions: (*a*) acetic acid and other materials boiling below 95°/16 mm.; (*b*) ethyl cyanoacetate, b.p. 95–110°/16 mm.; (*c*) intermediate, b.p. 110–124°/16 mm.; and (*d*) ethyl *sec*-butylidenecyanoacetate, b.p. 124–126°/16 mm., n_D^{25} 1.4640–1.4648. Fraction *d* amounts to 117–122 g., and refractionation of fraction *c* yields an additional 18–24 g.; total yield, 135–146 g. (81–87.5%) (Note 4).

B. *Ethyl 3-benzyl-2-cyano-3-methylpentanoate.* A 2-l. three-necked round-bottomed flask, fitted with a tantalum wire Hershberg stirrer, a condenser, and a separatory funnel, is arranged for use of a nitrogen atmosphere.[2] Magnesium (19.2 g., 0.79 g.-atom) and 100 ml. of dry ether[3] are placed in the flask, and a solution of 100 g. (91 ml., 0.79 mole) of benzyl chloride in 500 ml. of dry ether is added in a period of 1.5–2.0 hours, with stirring, while the mixture boils spontaneously. The mixture is boiled for 15 minutes after completion of the addition, then a solution of 110 g. (0.66 mole) of ethyl *sec*-butylidenecyanoacetate in 130 ml. of benzene is added over a 30-minute period with spontaneous reflux. The reaction mixture is stirred and heated under reflux for an additional hour. A precipitate separates after about 30 minutes.

The reaction mixture is poured onto about 400 g. of cracked ice and is made acidic with 20% sulfuric acid. After two clear phases have formed the mixture is poured into a separatory funnel, and the lower layer is removed. This aqueous layer is extracted with two 100-ml. portions of benzene and discarded. The three organic extracts are washed separately and successively with 125 ml. of water and 125 ml. of saturated sodium chloride solution, then filtered successively through a layer of anhydrous sodium sulfate.

The combined extract (about 1 l.) is flash-distilled at atmospheric pressure from a 250-ml. Claisen flask. After the solvent and a small amount of fore-run (ca. 15 g., b.p. 45°/3 mm.) have been removed, the product is distilled to yield 157–162 g. (92–95%), b.p. 150–162°/3 mm. (bath temperature, 180–190°), n_D^{25} 1.5053–1.5063 (Notes 5, 6, and 7).

C. *3-Benzyl-3-methylpentanenitrile.* Sixty-seven grams of potassium hydroxide is dissolved by heating in 360 ml. of ethylene glycol and is added to a 1-l. round-bottomed flask containing 155 g. (0.6 mole) of ethyl 3-benzyl-2-cyano-3-methylpentanoate (above). A condenser is attached with a rubber stopper, and the mixture is heated under gentle reflux for 3 hours (Note 8). The resulting two-phase mixture is cooled, diluted with 350 ml. of water, and extracted with three portions of ether (250 ml., 100 ml., 100 ml.). The three extracts are washed successively with 100 ml. of water and 100 ml. of saturated sodium chloride solution, then filtered through a layer of anhydrous sodium sulfate (Note 9). The combined extracts are flash-distilled at atmospheric pressure from a 250-ml. Claisen flask to remove the ether. The residue is distilled at reduced pressure to furnish 102–105 g. (91–93%) of nitrile, b.p. 150–160°/11 mm. (bath temperature, 190–200°), n_D^{25} 1.5111–1.5128 (Notes 10 and 11).

D. *3-Benzyl-3-methylpentanoic acid.* A solution of 112 g. of potassium hydroxide in 400 ml. of ethylene glycol is added to 93.6 g. (0.5 mole) of 3-benzyl-3-methylpentanenitrile in a 1-l. round-bottomed copper or stainless-steel flask. A condenser with a rubber stopper is attached, and the solution is heated under brisk reflux for 6 hours (Note 12). The reaction mixture is cooled, diluted with 400 ml. of water, and extracted with three portions of ether (250 ml., 100 ml., 100 ml.). The ether extracts are washed successively with two 75-ml. portions of water and then discarded (Note 13).

The combined aqueous phases are acidified to Congo red with 200 ml. of concentrated hydrochloric acid and extracted with three portions of benzene (200 ml., 75 ml., 75 ml.). The benzene extracts are washed successively with 100 ml. of water and 100 ml. of saturated sodium chloride solution, then filtered through anhydrous sodium sulfate. The combined extract is flash-distilled from a 250-ml. Claisen flask at atmospheric pressure (bath temperature, up to 160°). The residue is distilled at reduced pressure to give 94–96 g. (91–93%) of acid; b.p. 173–177°/7 mm. (bath temperature, 207–220°), n_D^{25} 1.5160–1.5163 (Notes 14 and 15).

2. Notes

1. Ethyl cyanoacetate was obtained from Kay-Fries Chemicals, 180 Madison Avenue, New York, New York.

2. The submitters used a Barrett Distilling Receiver, Corning No. 3622, Corning Glass Works, Corning, New York.

3. The submitters used a 60-cm. heated Vigreux column to effect this fractionation. The checkers used a similar column with partial take-off head.

4. Fractions *b–d* consist entirely of ethyl cyanoacetate and the product. Pure ethyl cyanoacetate and ethyl *sec*-butylidenecyanoacetate have n_D^{25} 1.4151 and 1.4650, respectively. The purity of fractions *b–d* can be estimated by their indexes of refraction, which are proportional to the weight per cent.

5. The pure product obtained by fractional distillation has n_D^{25} 1.5052. The product obtained by distillation from a Claisen flask is contaminated mainly with bibenzyl, b.p. 122–125°/3 mm., f.p. 44°. The purity of the product can be estimated by determination of the saponification equivalent in ethanol.

6. The use of dibenzylcadmium gave no improvement in yield.

7. Phenylmagnesium bromide gives a 79% yield of product, b.p. 178–180°/11 mm., n_D^{25} 1.5063; and *n*-propylmagnesium bromide gives 33–42% yields, b.p. 150–153°/22 mm., n_D^{25} 1.4429, of alkylation product when essentially the same procedure is used.

The yield obtained with *n*-propylmagnesium bromide depends upon the efficiency of separation from the reduction product, ethyl *sec*-butylcyanoacetate, b.p. 126°/22 mm., n_D^{25} 1.4277.[4]

8. After 30 minutes of reflux the second phase begins to separate. The formation of this nitrile layer is probably complete after 2.5–3.0 hours. A small amount of solid, presumably ammonium carbonate, collects in the condenser during the heating.

9. When the combined aqueous washes from three runs were acidified, extracted, and distilled, there was obtained 1.8 g. of 3-benzyl-3-methylpentanoic acid, n_D^{25} 1.5158.

10. This nitrile is contaminated with some lower-boiling bibenzyl and some higher-boiling amide. The pure nitrile, obtained by fractional distillation, has n_D^{25} 1.5110.

11. Hydrolyses of ethyl 2-cyano-3-methyl-3-phenylpentanoate and ethyl 2-cyano-3-ethyl-3-methylhexanoate (cf. Note 7) by essentially this procedure gave 71% (b.p. 149–151°/16 mm., n_D^{25} 1.5149) and 68% (b.p. 103–104°/31 mm., n_D^{25} 1.4291) yields of nitriles, respectively. In the second case, about 12% additional yield of nitrile could be obtained from the acidic fraction, which contains some undecarboxylated product, 2-cyano-3-ethyl-3-methylhexanoic acid.

12. The two-phase solution becomes homogeneous after 1.5–2.0 hours of boiling. This alkaline solution is very corrosive, and a glass flask can be used only a few times in this reaction. A stainless-steel or copper flask is preferable.

13. If emulsions are encountered, the addition of a few milliliters of saturated aqueous sodium chloride clears them readily. The combined ether extracts contain 4–5 g. of solid, neutral material. This product is mainly bibenzyl, b.p. 138–143°/7 mm., f.p. 40°.

14. The best sample of this acid obtained by fractional distillation had n_D^{25} 1.5160; neut. equiv., 207.3 (calcd., 206.3).

15. Hydrolyses of 3-methyl-3-phenylpentanenitrile and 3-ethyl-3-methylhexanenitrile (cf. Note 11) by the described procedure gave 88% and 95% yields of 3-methyl-3-phenylpentanoic acid (b.p. 190–194°/26 mm., n_D^{25} 1.5182) and 3-ethyl-3-methyl hexanoic acid (b.p. 136–137°/15 mm., n_D^{25} 1.4377), respectively.

3. Method of Preparation

Ethyl *sec*-butylidenecyanoacetate has been prepared by this condensation using various amino acids,[5] ammonium acetate,[6] sodium sulfate-piperidine,[7] and zinc chloride-aniline.[8]

The ethyl 3-benzyl-2-cyano-3-methylpentanoate, 3-benzyl-3-methylpentanenitrile, and 3-benzyl-3-methylpentanoic acid preparations follow the procedure given by Prout, Huang, Hartman, and Korpics.[9]

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[1] Department of Chemistry, De Paul University, Chicago 14, Illinois.

[2] Cason and Rapoport, *Laboratory Text in Organic Chemistry*, p. 312, Prentice-Hall, New York, New York, 1950; cf. *Org. Syntheses* Coll. Vol. **3**, 601 (1955).

[3] Cason and Rapoport, *Laboratory Text in Organic Chemistry*, p. 319, Prentice-Hall, New York, New York, 1950.

[4] Prout, *J. Am. Chem. Soc.*, **74**, 5915 (1952).

[5] Prout, *J. Org. Chem.*, **18**, 928 (1953).

[6] Cope, Hofmann, Wyckoff, and Hardenbergh, *J. Am. Chem. Soc.*, **63**, 3452 (1941).

[7] Cowan and Vogel, *J. Chem. Soc.*, **1940**, 1528.

[8] Scheiber and Meisel, *Ber.*, **48**, 259 (1915).

[9] Prout, Huang, Hartman, and Korpics, *J. Am. Chem. Soc.*, **76**, 1911 (1954).

p-BROMOMANDELIC ACID

(Mandelic acid, *p*-bromo)

$$p\text{-BrC}_6\text{H}_4\text{COCH}_3 + 2\text{Br}_2 \rightarrow p\text{-BrC}_6\text{H}_4\text{COCHBr}_2 + 2\text{HBr}$$

$$p\text{-BrC}_6\text{H}_4\text{COCHBr}_2 + 3\text{NaOH} \rightarrow p\text{-BrC}_6\text{H}_4\text{CHOHCOONa} + 2\text{NaBr} + \text{H}_2\text{O}$$

$$p\text{-BrC}_6\text{H}_4\text{CHOHCOONa} + \text{HCl} \rightarrow p\text{-BrC}_6\text{H}_4\text{CHOHCOOH} + \text{NaCl}$$

Submitted by J. J. Klingenberg.[1]
Checked by R. T. Arnold and C. D. Wright.

1. Procedure

p,α,α-Tribromoacetophenone. In a 1-l. three-necked flask (Note 1) equipped with an efficient mechanical stirrer, a dropping funnel, and a gas outlet leading to a hood or trap are placed 100 g. (0.5 mole) of *p*-bromoacetophenone (Note 2) and 300 ml. of glacial acetic acid. The resulting solution is stirred and cooled to 20°, and a solution of 26 ml. (0.5 mole) of bromine in 100 ml. of glacial acetic acid is added dropwise (Note 3). Crystals of the mono-α-brominated derivative separate during the addition, which requires about 30 minutes. When the addition is completed, a second solution of 26 ml. (0.5 mole) of bromine in 100 ml. of glacial acetic acid is added dropwise. Slight heating may be necessary to keep the reaction proceeding, as indicated by decolorization of the bromine, but the temperature should be kept as near 20° as possible. During the addition, which requires about 30 minutes, the solid dissolves and crystals of the di-α,α-brominated derivative appear toward the end of the addition. The flask is heated to dissolve the contents, which are transferred, preferably in a hood, to a 1-l. beaker and cooled rapidly by means of an ice-water bath (Note 4). The mixture is filtered with suction (Note 5), and the solid is washed with 50% ethanol until colorless. The air-dried product has a slight pink cast and melts at 89–91°. The yield is 130–135 g. (73–76%) (Note 6). A pure, white solid melting at 92–94° is obtained by recrystallization from ethanol, but the initial product is sufficiently pure for the next step.

p-Bromomandelic acid. In a Waring-type blender are placed 89 g. (0.25 mole) of *p*,α,α-tribromoacetophenone and 100–150 ml. of cold water. The mixture is stirred for 10–15 minutes, and the contents are transferred to a 1-l. wide-mouthed bottle. The mixing vessel is rinsed with 150–200 ml. of ice-cold water. The material from the rinse is combined with the mixture in the bottle, and sufficient crushed ice is added to bring the temperature below 10°. One hundred milliliters of a chilled aqueous solution containing 50 g. of sodium hydroxide is added slowly while the bottle is rotated (Note 7). The contents are stored for approximately 4–5 days in a refrigerator (5°) and are shaken occasionally. During this time most of the solid dissolves, but a slight amount remains as a yellow sludge and the liquid assumes a yellow to amber color. The mixture is filtered, and the insoluble material is discarded. An excess of concentrated hydrochloric acid is added to the filtrate. The entire resulting mixture containing a white solid is extracted with three 200-ml. portions of ether. The ether extracts are combined, dried over anhydrous sodium sulfate, and filtered into a 1-l. flask. The ether is carefully removed by distillation using a hot-water bath to give a yellow oil which solidifies when cooled. The product is recrystallized from 500 ml. of benzene. The crystals are collected by filtration and washed with benzene until the filtrate is colorless. The air-dried product (Note 8) weighs 40–48 g. (69–83% based on *p*,α,α-tribromoacetophenone), m.p. 117–119° (Note 9). A second recrystallization from 500 ml. of benzene is sometimes necessary.

2. Notes

1. The use of ground-glass equipment is desirable but not necessary.

2. The preparation of *p*-bromoacetophenone is described in *Organic Syntheses.*[2] The compound is also available from Eastman Kodak Company.

3. Sometimes the initation of the reaction is slow. The reaction may be started by heating the solution until the bromine is decolorized (approximately 45°), after which the reaction will proceed normally at 20°.

4. The checkers found that maximum yields of product were obtained when cooling was carried to the point where crystallization of the solvent commenced. The trace of crystalline solvent quickly melts during the filtering procedure.

5. These compounds are lachrymatory and should be kept away from the eyes.

6. An additional quantity of less pure material can be isolated from the glacial acetic acid mother liquid and alcohol filtrates by evaporation of the solvent. This, after recrystallization from ethanol, amounts to 15–30 g.

7. It is important that the reaction mixture be kept cold at this point. The amount of sludge and colored material increases as the temperature increases.

8. The last traces of benzene leave very slowly and if present lower the melting point. The product should be thoroughly dried in air or on a clay plate before the melting point is taken.

9. Under similar conditions, *p*-chloromandelic acid melting at 119–120° was obtained from *p*-chloroacetophenone in 54% yield and *p*-iodomandelic acid melting at 135–136° from *p*-iodoacetophenone in 21% yield.

3. Methods of Preparation

p-Bromomandelic acid has been prepared by the bromination of *p*-bromoacetophenone followed by alkaline hydrolysis;[3] by the alkaline hydrolysis of the product formed by the addition of chloral to *p*-bromophenylmagnesium bromide;[4] and by the condensation of bromobenzene and ethyl oxomalonate in the presence of stannic chloride followed by hydrolysis and decarboxylation.[5] *p*-Bromomandelic acid is a valuable reagent in the analyses of zirconium and hafnium.[6]

[1] Xavier University, Cincinnati, Ohio.

[2] *Org. Syntheses* Coll. Vol. **1**, 109 (1941).

[3] Collet, *Bull. soc. chim. France,* [3] **21**, 67 (1899).

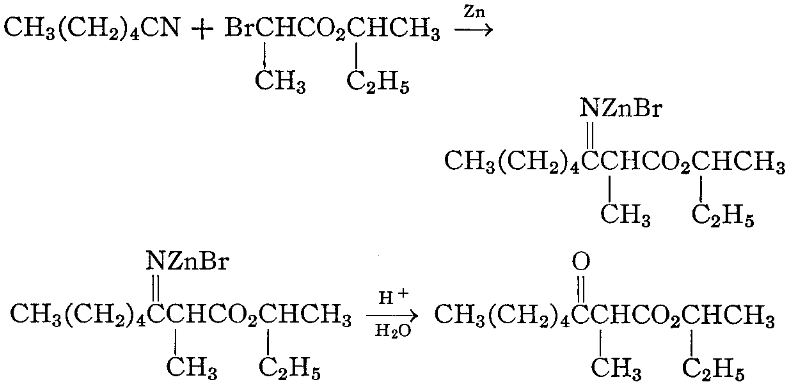
[4] Hebert, *Bull. soc. chim. France,* [4] **27**, 45 (1920).

[5] Riebsomer, Baldwin, Buchanan, and Burkett, *J. Am. Chem. Soc.*, **60**, 2974 (1938).

[6] Hahn, *Anal. Chem.*, **23**, 1259 (1951); Klingenberg and Papucci, *Anal. Chem.*, **24**, 1861 (1952).

sec-BUTYL *α*-*n*-CAPROYLPROPIONATE

(Octanoic acid, 2-methyl-3-oxo-, *sec*-butyl ester)



$$CH_3(CH_2)_4CN + \underset{CH_3}{BrCH}CO_2\underset{C_2H_5}{CH}CH_3 \xrightarrow{Zn} CH_3(CH_2)_4\overset{NZnBr}{\overset{\|}{C}}\underset{CH_3}{CH}CO_2\underset{C_2H_5}{CH}CH_3$$

$$CH_3(CH_2)_4\overset{NZnBr}{\overset{\|}{C}}\underset{CH_3}{CH}CO_2\underset{C_2H_5}{CH}CH_3 \xrightarrow[H_2O]{H^+} CH_3(CH_2)_4\overset{O}{\overset{\|}{C}}\underset{CH_3}{CH}CO_2\underset{C_2H_5}{CH}CH_3$$

Submitted by Kenneth L. Rinehart.[1]
Checked by John C. Sheehan and J. Iannicelli.

1. Procedure

A 2-l. three-necked round-bottomed flask is fitted with a condenser arranged for distillation, a 200-ml. dropping funnel, and a mercury-sealed mechanical stirrer. Connections are most conveniently made with ground-glass joints, and the flask is heated on a steam cone. Cupric bromide (0.4 g.), 39.2 g. (0.60 mole) of freshly sand-papered zinc foil cut into narrow strips, and 1.2 l. of benzene previously dried over sodium are added to the flask. To dry the apparatus and contents, 300 ml. of benzene is slowly distilled from the flask with stirring. Heating is interrupted, and the condenser is quickly arranged for reflux and fitted with a calcium chloride drying tube. To the flask are added rapidly with stirring 38.9 g. (0.40 mole) of *n*-capronitrile (Note 1) and 125.4 g. (0.60 mole) of *sec*-butyl *α*-bromopropionate (Note 2). Refluxing is resumed, and after a 3–5 minute induction period blackening of the zinc surface and clouding of the solution are noted as the first signs of reaction. Heating is maintained a total of 45 minutes, after which the solution is cooled for 15 minutes in an ice bath (Note 3).

To the cooled solution is added with vigorous stirring 400 ml. of ice-cold 12 *N* sulfuric acid. The ice bath is removed, and stirring is continued at room temperature for a total of 2 hours (Note 4). The reaction mixture is poured into a 2-l. separatory funnel; after separation, the aqueous lower layer is drained into a 2-l. separatory funnel containing 800 ml. of water which has been used to wash the reaction flask. The aqueous layer is extracted twice with 200-ml. portions of benzene which have also been employed to rinse the reaction flask. The original organic layer and the combined benzene extracts are kept separate and are washed successively with 400-ml. portions of water, saturated sodium bicarbonate solution, and again with water. The two organic portions are combined and allowed to stand over anhydrous sodium sulfate until clear. The solvent is removed at atmospheric pressure by flash distillation through a fractionating column (Note 5). For this operation, a side-arm distilling flask equipped with a dropping funnel is heated by an oil bath whose temperature is maintained at 140–150°. After all the solvent has been added, the dropping funnel is replaced by a capillary, and the last of the solvent is removed at reduced pressure furnished by a water pump. Finally, an oil pump is attached and the product is fractionated at about 5 mm. pressure (Note 6). After a small fore-run, *sec*-butyl α-*n*-caproylpropionate is obtained as a clear liquid; b.p. 112–114°/4.5 mm. (134–136°/12 mm.), n_D^{25} 1.4293 (Notes 7 and 8). The yield is 46.0–52.9 g. (50–58% based on *n*-capronitrile) (Note 9).

2. Notes

1. Commercial *n*-capronitrile (Eastman Kodak White Label) is distilled through a fractionating column before use; b.p. 161–163°, n_D^{25} 1.4052.

2. α-Bromoesters are severe lachrymators, and it is necessary to conduct reactions involving them in a well-ventilated hood. *sec*-Butyl α-bromopropionate is prepared from commercially available ethyl α-bromopropionate (Sapon Laboratories, Inc., 543 Union Street, Brooklyn 15, New York) by transesterification with *sec*-butyl alcohol using sulfuric acid catalyst. The product boils at 97–98°/39 mm. and has n_D^{25} 1.4420. Darkening of the α-bromoester is prevented by storage over a few drops of mercury.

3. Unreacted zinc usually remains at this point, and the solution is yellow to brown. Most of the color is discharged on subsequent addition of the acid.

4. With 3-methylnonanoic nitrile it is necessary to continue the stirring in sulfuric acid for an additional period; a total of 19 hours is sufficient.

5. A 50 cm. by 8 mm. simple Podbielniak column [2] with partial-reflux head is adequate for this and subsequent distillations.

6. Fractionation at higher pressures and temperatures leads to some thermal decomposition of the product.

7. An analytical sample of a redistilled center cut had n_D^{25} 1.4302.

8. β-Ketoesters with alkyl substituents in the α-position give a blue-violet color with ferric chloride.[3] Copper chelates of the α-alkyl-β-ketoesters could not be isolated. The corresponding 5-pyrazolones, although often difficultly crystallizable, appear to be the most suitable derivatives. The 5-pyrazolone from *sec*-butyl α-*n*-caproylpropionate is prepared according to von Auwers and Dersch [4] and has melting point 80.4–82.9°.

9. This method is suitable for the preparation of mono- and di-α-substituted β-ketoesters. Bromoacetates fail in this reaction. Yields with ethyl α-bromopropionate are considerably lower (30–36% with capronitrile); however, ethyl esters are useful for higher-molecular-weight compounds whose *sec*-alkyl esters are cracked by distillation. With 3-pentyl α-bromopropionate, the yields are slightly higher (53–60% with capronitrile). Both aromatic and aliphatic nitriles are suitable; benzonitrile gives yields comparable to those obtained with capronitrile. Alkyl substitution in the α- and β-positions (cf. Note 4) of aliphatic nitriles lowers the yield to 29% and 38%, respectively; γ-substitution has no effect.

3. Methods of Preparation

The procedure is essentially that of Horeau and Jacques[5] as modified by Cason, Rinehart, and Thornton.[6] The reaction described is that discovered by Blaise[7] and is more extensively discussed in the second-named paper. Ethyl α-*n*-caproylpropionate has been prepared by the alkylation of ethyl *n*-caproylacetate with methyl iodide in the presence of sodium ethoxide.[8] This method would not be expected to yield a pure product owing to contamination with starting ketoester and disubstituted ketoester.

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[1] University of California, Berkeley, California.

[2] Podbielniak, *Ind. Eng. Chem., Anal. Ed.*, **3**, 177 (1931); **5**, 119 (1933).

[3] Henecka, *Ber.*, **81**, 188 (1948).

[4] von Auwers and Dersch, *Ann.*, **462**, 115 (1928).

[5] Horeau and Jacques, *Bull. soc. chim. France*, **1947**, 58.

[6] Cason, Rinehart, and Thornton, *J. Org. Chem.*, **18**, 1594 (1953).

[7] Blaise, *Compt. rend.*, **132**, 478, 978 (1901); Blaise and Courtot, *Bull. soc. chim. France*, [3] **35**, 599 (1906).

[8] Locquin, *Bull. soc. chim. France*, [3] **31**, 596 (1904).

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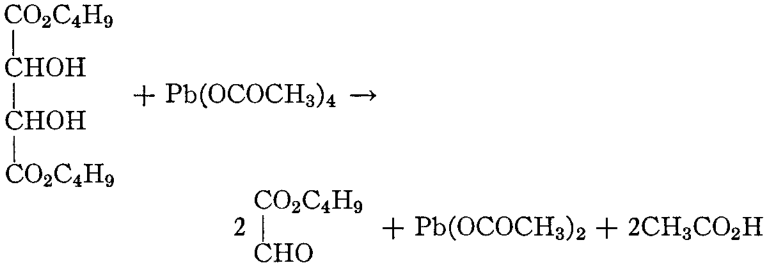
n-BUTYL GLYOXYLATE

(Glyoxylic acid, *n*-butyl ester)



$$\begin{array}{l} CO_2C_4H_9 \\ | \\ CHOH \\ | \\ CHOH \\ | \\ CO_2C_4H_9 \end{array} + Pb(OCOCH_3)_4 \rightarrow 2\begin{array}{l} CO_2C_4H_9 \\ | \\ CHO \end{array} + Pb(OCOCH_3)_2 + 2CH_3CO_2H$$

Submitted by Frank J. Wolf and John Weijlard.[1]
Checked by N. J. Leonard and L. A. Miller.

1. Procedure

In a 3-l. three-necked round-bottomed flask provided with a Hershberg stirrer and a thermometer are placed 1.25 l. of reagent-grade benzene and 325 g. (1.24 moles) of di-*n*-butyl *d*-tartrate (Note 1). The mixture is stirred rapidly, and 578 g. (1.30 moles) of lead tetraacetate (Note 2) is added over a period of about 25 minutes. The temperature is maintained below 30° by occasional cooling with cold water. After the addition is complete, the mixture is stirred for 1 hour, during which time the gummy salts become crystalline. The salts are removed by filtration with suction and washed with 500 ml. of benzene. The benzene and acetic acid are removed from the filtrate by distillation at 65°/50 mm. The residue is distilled at 20 mm. under nitrogen introduced through an ebullator, using a Vigreux column (2 by 30 cm.), and the fraction boiling between 65° and 79°/20 mm. (main portion at 68–74°) is collected as product. The crude *n*-butyl glyoxylate, which weighs 247–280 g. (77–87%), n_D^{20} 1.442–1.443, d_4^{25} 1.085, is satisfactory for most purposes (Note 3).

2. Notes

1. The di-*n*-butyl *d*-tartrate used was the purest grade from Eastman Kodak Company, m.p. 20–22°.

2. Lead tetraacetate was obtained from the G. Frederick Smith Chemical Company, Columbus, Ohio. It may also be prepared by the procedure described in *Inorganic Syntheses*.[2]

3. The product undergoes autoxidation and should be stored under nitrogen. Further purification may be effected by a second fractional distillation under nitrogen at reduced pressure. The product decomposes on boiling (159–161°) at atmospheric pressure.

3. Methods of Preparation

n-Butyl glyoxylate has not been described previously. *Anal.* Calcd. for $C_6H_{10}O_3$: C, 55.37; H, 7.75. Found: C, 54.95; H, 7.83. Ethyl glyoxylate has been prepared in good yield by oxidation of ethyl tartrate with red lead oxide[3] or sodium bismuthate.[4] These papers describe isolation of ethyl glyoxylate as carbonyl derivatives.

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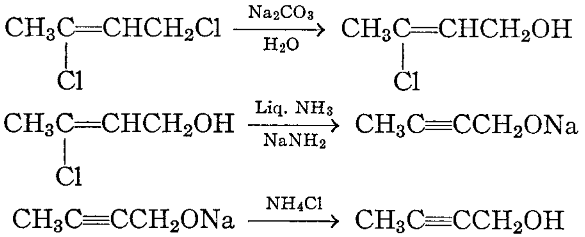
[1] Merck and Company, Rahway, New Jersey.

[2] *Inorg. Syntheses*, **1**, 47 (1939).

[3] Hamamura, Suzumoto, and Hayashima, *J. Agr. Chem. Soc. Japan*, **22**, 24 (1948) [*C. A.*, **46**, 10108 (1952)].

[4] Rigby, *Nature*, **164**, 185 (1949).

2-BUTYN-1-OL



$$CH_3\underset{\overset{|}{Cl}}{C}{=}CHCH_2Cl \xrightarrow[H_2O]{Na_2CO_3} CH_3\underset{\overset{|}{Cl}}{C}{=}CHCH_2OH$$

$$CH_3\underset{\overset{|}{Cl}}{C}{=}CHCH_2OH \xrightarrow[NaNH_2]{\text{Liq. } NH_3} CH_3C{\equiv}CCH_2ONa$$

$$CH_3C{\equiv}CCH_2ONa \xrightarrow{NH_4Cl} CH_3C{\equiv}CCH_2OH$$

Submitted by P. J. Ashworth, G. H. Mansfield, and M. C. Whiting.[1]
Checked by John C. Sheehan, George Buchi, and Walfred S. Saari.

1. Procedure

Caution! The experimental procedure involving liquid ammonia should be conducted in a hood.

In a 3-l. three-necked round-bottomed flask fitted with a reflux condenser and a mercury-sealed stirrer, 250 g. (2 moles) of 1,3-dichloro-2-butene (Note 1) and 1.25 l. of 10% sodium carbonate are heated at reflux temperature for 3 hours. The 3-chloro-2-buten-1-ol is extracted with three 300-ml. portions of ether, which are then dried over anhydrous magnesium sulfate. The ether is removed by distillation through a 20-cm. Fenske column, and the residue is distilled from a 250-ml. Claisen flask, yielding 134 g. (63%) of 3-chloro-2-buten-1-ol, b.p. 58–60°/8 mm., n_D^{20} 1.4670.

A solution of sodium amide in liquid ammonia is prepared according to a procedure previously described[2] using a 4-l. Dewar flask equipped with a plastic cover (Note 2) and a mechanical stirrer. Anhydrous liquid ammonia (3 l.) is introduced through a small hole in the plastic cover, and 1.5 g. of hydrated ferric nitrate is added followed by 65 g. (2.8 gram atoms) of clean, freshly cut sodium. The mixture is stirred until all the sodium is converted into sodium amide, after which 134 g. (1.26 moles) of 3-chloro-2-buten-1-ol is added over a period of 30 minutes. The mixture is stirred overnight, then 148 g. (2.8 moles) of solid ammonium chloride is added in portions at a rate that permits control of the exothermic reaction. The mixture is transferred to a metal bucket (5-l., preferably of stainless steel) and allowed to stand overnight in the hood while the ammonia evaporates. The residue is extracted thoroughly with five 250-ml. portions of ether, which is removed by distillation through a 20-cm. Fenske column. Distillation of the residue yields 66–75 g. (75–85%) of 2-butyn-1-ol, b.p. 55°/8 mm., n_D^{20} 1.4550 (Note 3).

2. Notes

1. 1,3-Dichloro-2-butene was obtained from Eastman Kodak Company. Redistillation of the crude material did not appreciably alter the yield in the first stage of the reaction.

2. The checkers used an ordinary flask, well insulated, for this reaction.

3. Others have reported b.p. 91–93°/50 mm., n_D^{25} 1.4630;[3] b.p. 160.5°, n_D^{25} 1.4635;[4] b.p. 160–161°, n_D^{25} 1.4635, for 3-chloro-2-buten-1-ol, and b.p. 87–88°/100 mm., n_D^{25} 1.4520;[3] b.p. 140–141°, n_D^{25} 1.4517[5] for 2-butyn-1-ol.

3. Methods of Preparation

2-Butyn-1-ol has been prepared as above for the first stage[3,4,5] but using aqueous sodium hydroxide[3] and alcoholic potassium hydroxide[5] for the second stage. Earlier workers[6,7] employed the reaction between propynylmagnesium bromide and formaldehyde.

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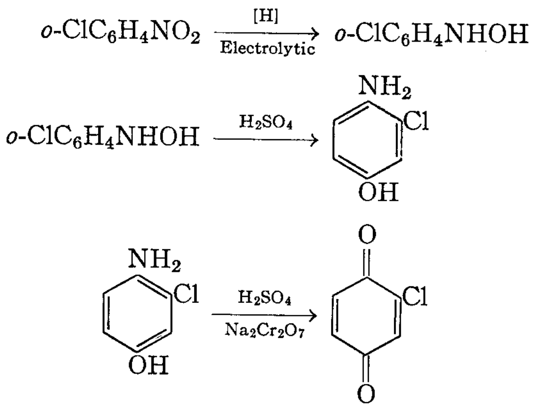
[1] Victoria University of Manchester, Manchester, England.

[2] *Org. Syntheses*, **30**, 72 (1950).
[3] Hatch and Nesbitt, *J. Am. Chem. Soc.*, **72**, 729 (1950).
[4] Hatch and Hudson, *J. Am. Chem. Soc.*, **72**, 2505 (1950).
[5] Hatch and Chiola, *J. Am. Chem. Soc.*, **73**, 360 (1951).
[6] Yvon, *Compt. rend.*, **180**, 748 (1925).
[7] Hurd and Cohen, *J. Am. Chem. Soc.*, **53**, 1074 (1931).

CHLORO-*p*-BENZOQUINONE

(*p*-Quinone, chloro-)



$$o\text{-ClC}_6\text{H}_4\text{NO}_2 \xrightarrow[\text{Electrolytic}]{[\text{H}]} o\text{-ClC}_6\text{H}_4\text{NHOH}$$

Submitted by R. E. Harman.[1]
Checked by N. J. Leonard and R. W. Fulmer.

1. Procedure

A. *Apparatus.* The reduction is carried out in a 400-ml. beaker. The anode, a cylinder of sheet lead 3 in. in height and 2.25 in. in diameter, rests on the bottom of the beaker. Clamped inside the anode and extending almost to the bottom of the beaker is the catholyte chamber, a porous cup (Note 1) 5 in. deep and 1.75 in. in diameter. Clamped securely inside the cup and about 0.25 in. above its inside bottom surface is the cathode, a cylinder of 25-gauge sheet copper 6 in. long and 1.25 in. in diameter. It is provided with a row of seven vertical slots 0.25 in. wide and 1.25 in. long, evenly spaced around its circumference; the lower ends of the slots are about 2.5 in. from the bottom of the cathode (Note 2). Both electrodes are provided with binding posts for connection to the circuit. A stirrer is constructed with two double propeller blades attached to the shaft, one about 1.5 in. above the other, at a pitch that will direct the flow of liquid downward. The mechanically driven stirrer is set to run deep inside the cathode (Note 3).

The current may be drawn from a commercially available battery charger (Note 4) or from a storage battery, each capable of operating at about 6 volts. Experiment has shown that the considerable ripple in the output of the charger has no adverse effect on the reduction. A transformer in the input to the charger, or a variable resistance in the battery circuit, and a 0–3 ampere range d.c. ammeter complete the apparatus.

B. *Reduction of o-chloronitrobenzene.* The stirrer is set in position carefully inside the cathode, which is clamped in place at the top. The porous cup, previously impregnated with the electrolyte, is charged with 11.5 g. (0.073 mole) of *o*-chloronitrobenzene (Note 5) and about 80 ml. of a mixture of acetic acid (70 ml.), concentrated sulfuric acid (22 ml.), and water (8 ml.) (Note 6). The cup is then clamped securely in position, and the beaker containing the anode is supported just clear of the bottom of the porous cup and filled with the same solution of aqueous sulfuric and acetic acids to the same level as the liquid inside the cup. The stirrer is started, the current turned on, and the system observed for a few minutes until the current has become stable. It is then adjusted at some convenient value no greater than 2 amperes.

The temperature will rise slowly and should be maintained at 30–45° throughout the reduction, with cooling as necessary. The system requires no attention while in operation except for occasional inspection and possibly the addition of a few milliliters of 90% acetic acid to maintain the surface of the catholyte at the desired level (Note 7).

C. *Oxidation of 4-amino-3-chlorophenol.* When the reduction is complete (Note 8), the system is disassembled, the catholyte poured into a flask, and the apparatus rinsed with hot water into the same flask. The combined catholyte and washings are extracted with ether in a continuous-type liquid-liquid extractor to remove the acetic acid almost completely (Note 9). The residual aqueous acid solution of the aminophenol (Note 10) is made up to 4 *N* in sulfuric acid by adding 20 ml. of concentrated sulfuric acid and diluting with water to 400 ml.

At room temperature there is added in one portion a solution of 11 g. (0.037 mole, 50% excess over the theoretical amount) of sodium dichromate dihydrate in 20 ml. of water. A rise in temperature of some 6–7° will be observed; it is desirable to moderate the temperature by external cooling if it should rise above 35°.

After the mixture has been allowed to stand at room temperature for at least an hour (Note 11), a few grams of clean sand are added and the dark red mixture is filtered with suction. The filtrate is extracted with ether (100 ml., then 4–5 portions of about 30 ml. each), and each extract is used in turn to extract the filter cake.

The ether extracts are combined; the ether is removed by distillation (Note 12), and the dark red tarry residue subjected to steam distillation. Some 40–50 ml. of distillate is collected after solid quinone no longer appears in the condenser (total volume about 150 ml.).

There is obtained by filtration 5.0–5.5 g. (48–54%) of yellow chloro-*p*-quinone of m.p. 53–55°; ether extraction of the filtrate yields a further 1.0 g., which brings the total yield to 58–63% (Notes 12 and 13). Crystallization from a small volume of aqueous ethanol (85–90%) raises the melting point to 55–56°.

2. Notes

1. A Norton dense grade Alundum extraction thimble has been found suitable. Deposition of silicic acid in the interstices of the cup to decrease transfer of material is desirable. This is accomplished by soaking the cup for an hour in 20% water glass, draining off the excess, and then keeping the cup totally immersed for 3 hours in 20% aqueous sulfuric acid.[2] Finally, the cup is stored completely immersed in the electrolyte.

2. This cathode design, with the stirring described, is regarded as preferable to the combination used by Lukens[3] and much simpler in construction. It provides better dispersion of the organic material, a feature which is particularly necessary if these reductions are carried out in aqueous solution (Note 6).

3. Very rapid and efficient stirring is required to strip the intermediate *o*-chlorophenylhydroxylamine from the cathode so that the acid-catalyzed rearrangement to 4-amino-3-chlorophenol may occur rather than reduction of the substituted hydroxylamine to *o*-chloroaniline.

4. A Battery Booster, type 6-AC-4, manufactured by P. R. Mallory and Company, Inc., Indianapolis, Indiana, gave good service.

5. A grade equivalent to Eastman Kodak Company White Label was used. It has been found that the same results are obtained using *m*-chloronitrobenzene. Likewise, either *o*- or *m*-nitrotoluene may be used in the preparation of toluquinone (Note 13).

6. The submitter states that lower yields of quinones (50–65%) are obtained by using as the electrolyte 75% by weight aqueous sulfuric acid. The catholyte at the end of the reduction is diluted to about 500 ml. (4 *N* in sulfuric acid) and oxidized directly. The low solubility of the nitro compounds in the aqueous acid makes exceedingly efficient stirring a necessity, and the cell must be maintained at 50–60° during the reduction to keep the nitro compound molten and so promote the formation of a fine emulsion. Solid aminophenol sulfate sometimes crystallizes near the end of the reduction, and evolution of hydrogen near the end of the run may force the pasty material out the top of the porous cup. In general, these difficulties are more troublesome than the continuous extraction necessitated by the use of acetic acid in the catholyte.

7. In operation, a flood of electrolyte should be observable pouring over the lower ends of the slots in the cathode.

8. Complete reduction of the nitro compound is assured by the use of about 1.2 equivalents of current (9.4 ampere-hours), but a larger excess of current is no disadvantage.

9. It has been found satisfactory to continue the extraction for 30 minutes after the volume of the aqueous phase no longer decreases visibly. Saturated aqueous sodium bicarbonate washes may be used to effect removal of the acetic acid from ether solutions of alkyl quinones. The cascade distribution apparatus devised by Kies and Davis [4] is useful for this purpose. As halogenated quinones have been found to be unstable to bicarbonate, the acetic acid must be removed before oxidation of the corresponding aminophenols.

10. It has been found that the sulfates of the aminophenols may be obtained in yields about the same as those recorded for the quinones by concentrating the aqueous catholytes under reduced pressure after removal of the acetic acid.

11. It is recommended that the oxidation mixture be stored in a refrigerator if more than 6–8 hours must elapse before the work-up is completed.

12. Prolonged heating after removal of the ether may lead to sublimation of the product, with resulting lower yield.

13. Essentially the same procedure, with alteration only in the temperature during the oxidation, is stated by the submitter to be satisfactory for the preparation of several other *p*-benzoquinones. For *p*-benzoquinone itself and for toluquinone (both in 80% yield) the oxidation is best carried out at 5–10°; for 3-chlorotoluquinone (70% yield), at 15–20°; for 2,5-dichloroquinone (50% yield), at 55–60°. In the last case, some of the weakly basic aminophenol is ether extracted along with the acetic acid; it may be recovered by distilling most of the ether and acetic acid under reduced pressure, extracting the dark residue with two 25-ml. portions of 1 *N* sodium hydroxide, and making the alkaline extract neutral or slightly acid with sulfuric acid. Normal oxidation is carried out after combining this suspension of aminophenol with the original aqueous solution.

The low vapor pressure of 2,5-dichloroquinone precludes the use of steam distillation; however, the quinone precipitates directly from the oxidation mixture as a tan solid and may be purified readily by sublimation, followed by crystallization from ethanol. An excellent sublimation apparatus that will easily handle 10-g. quantities of this quinone has been described.[5]

This method has given only 25% yield of methoxyquinone which is highly sensitive to acid and requires a special isolation procedure.[6]

3. Methods of Preparation

The present method is the result of a study by Cason, Harman, Goodwin, and Allen.[6,7] The sequence of electrolytic reduction followed by oxidation has been used for the preparation of 5-bromotoluquinone,[8] 5-chlorotoluquinone,[9] and 3-chlorotoluquinone.[10] The preparation of an intermediate *p*-aminophenol from the corresponding aromatic nitro compound by electrolytic reduction is a useful general method.[11–18] Chloro-*p*-quinone has been prepared by acid dichromate oxidation of chlorohydroquinone [19–22] or 2-chloro-4-aminophenol.[23,24] It has been shown that pure chloro-*p*-quinone is obtained only with some difficulty when chlorohydroquinone is used.[7]

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[1] Department of Chemistry, University of California, Berkeley, California.

[2] Swann, "Electrolytic Reductions," in Weissberger, *Technique of Organic Chemistry*, Vol. 2, p. 143, Interscience Publishers, New York, New York, 1948.

[3] Lukens, *Ind. Eng. Chem.*, **13**, 562 (1921).

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[6] Harman and Cason, *J. Org. Chem.*, **17**, 1047, 1058 (1952).

[7] Cason, Harman, Goodwin, and Allen, *J. Org. Chem.*, **15**, 860 (1950).

[8] Gattermann, *Ber.*, **27**, 1931 (1894).

[9] Raiford, *Am. Chem. J.*, **46**, 445 (1911).

[10] Cason, Allen, and Goodwin, *J. Org. Chem.*, **13**, 403 (1948).

[11] Gattermann, *Ber.*, **26**, 1844 (1893).

[12] Gattermann and Koppert, *Chem. Ztg.*, **17**, 210 (1893).

[13] Piccard and Larsen, *J. Am. Chem. Soc.*, **40**, 1090 (1918).

[14] Brigham and Lukens, *Trans. Electrochem. Soc.*, **61**, 281 (1932).

[15] Fieser and Martin, *J. Am. Chem. Soc.*, **57**, 1840 (1935).

[16] Mann, Montonna, and Larian, *Trans. Electrochem. Soc.*, **69**, 367 (1936).

[17] Dey, Govindachari, and Rajagopalan, *J. Sci. Ind. Research* (*India*), **4**, 574 (1946) [*C. A.*, **40**, 4965 (1946)].

[18] Dey, Maller, and Pai, *J. Sci. Ind. Research* (*India*), **B7**, 113 (1948) [*C. A.*, **43**, 3730 (1949)].

[19] Levy and Schultz, *Ann.*, **210**, 145 (1881).

[20] den Hollander, *Rec. trav. chim.*, **39**, 481 (1920).

[21] Eckert and Endler, *J. prakt. Chem.*, (2) **104**, 83 (1922).

[22] Conant and Fieser, *J. Am. Chem. Soc.*, **45**, 2201 (1923).

[23] Kollrepp, *Ann.*, **234**, 14 (1886).

[24] van Erp, *Ber.*, **58**, 663 (1925).

N-CHLOROBETAINYL CHLORIDE

(Ammonium chloride, chloroformylmethyl, trimethyl-)

$$(CH_3)_3N(Cl)CH_2COOH + SOCl_2 \rightarrow (CH_3)_3N(Cl)CH_2COCl + SO_2 + HCl$$

Submitted by B. Vassel and W. G. Skelly.[1]
Checked by John C. Sheehan and J. Iannicelli.

1. Procedure

Caution! This preparation should be conducted in a good hood.

A 1-l. round-bottomed flask is equipped with an internal thermometer, a sealed stirrer, and a reflux condenser, the upper end of which is protected with a calcium chloride drying tube. In this flask are placed 307 g. (2 moles) of dry, pulverized betaine hydrochloride (Note 1) and 285 g. (174 ml., 2.4 moles) of thionyl chloride. The mixture is stirred and heated slowly. When the internal temperature reaches 68° copious evolution of sulfur dioxide and hydrogen chloride occurs, and the mass becomes pasty. The temperature is maintained with stirring at 68–70° for 1.5 hours (Note 2).

Warm (80°) dry toluene (150 ml.) is added to the melt, and stirring is continued for 5 minutes. The entire mass is quickly poured into a dry beaker (Note 3) and slowly stirred, manually, until the entire mass has crystallized (Note 4). The cool toluene is decanted rapidly, and 150 ml. of warm toluene is added. The mixture is heated sufficiently to melt the crystals (about 68°), then allowed to cool again with stirring. The toluene is decanted once more, and 150 ml. of hot (60°) dry benzene is added. The mass is melted once more, and cooled with stirring. The crystalline mass, with the benzene layer still covering it, is transferred rapidly to a Büchner funnel sufficiently large to hold all the contents of the beaker. The funnel is immediately covered with a rubber diaphragm, and suction is applied (Note 5). The crystals are quickly covered with 150 ml. of dry methylene chloride, dried with suction, and quickly transferred into a glass vacuum oven at 50° (Note 6). The yield of N-chlorobetainyl chloride is 337–344 g. (98–100%) of 98–100% purity if moisture was rigorously excluded (Note 7).

2. Notes

1. The betaine hydrochloride was obtained from International Minerals and Chemical Corporation. It was pulverized, dried at 105° for 3 hours, ground again, and dried once more at 105° for 3 hours.
2. The mixture should be fluid after about the first 20 minutes of heating. If at this stage the betaine hydrochloride has not completely lost its granular appearance it is probable that it had not been adequately dried or that the reaction temperature had been below 68°. If it is considered that the betaine hydrochloride had not been dry enough the reaction may be completed by adding an additional 41 g. (25 ml., 0.34 mole) of thionyl chloride and continuing the stirring and heating for 1.25 hours.
3. Success in the isolation of the pure acid chloride depends upon the rigorous exclusion of moisture. The acid chloride hydrolyzes to the hydrochloride with great rapidity when exposed to even traces of moist air. During the stirring of the warm melt, care must be exercised that a layer of toluene covers the melt at all times.
4. If the melt is permitted to crystallize without stirring, a hard glasslike layer forms which cannot be broken up without exposure to air.
5. The rubber diaphragm is sold by Fisher Scientific Company as Dental Dam. It is held in place by two strong rubber bands. The suction flask is protected from moisture by attachment of a calcium chloride drying tube to the vacuum line if a water aspirator is used.
6. The dried acid chloride is conveniently stored in about 25 bottles with tightly fitting plastic screw caps which are kept in a desiccator over phosphorus pentoxide. In this manner the acid chloride is exposed to a minimum of atmospheric moisture when reactions are run which require only part of the preparation.

7. The same yield and purity were obtained when 1229 g. (8 moles) of betaine hydrochloride was used. In this case the volumes of toluene, benzene, and methylene chloride do not have to be increased proportionally if narrow, tall beakers are used. About 300 ml. of each is sufficient.

3. Methods of Preparation

N-Chlorobetainyl chloride has been prepared by treating betaine hydrochloride with either thionyl chloride,[2] phosphorus pentachloride in acetyl chloride,[3,4] or phosphorus pentachloride in phosphorus oxychloride.[5] None of the patents mentions the instability of the acid chloride towards moisture or describes a method for the isolation of the pure product.

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[1] Central Research Laboratories, International Minerals and Chemical Corporation, Skokie, Illinois.

[2] Linch, U. S. pats. 2,359,862; 2,359,863 [*C. A.*, **39**, 2076, 2077 (1945)].

[3] Society of Chemical Industry of Basel, Brit. pats. 589,232; 590,727 [*C. A.*, **42**, 230, 210 (1948)].

[4] Ruzicka and Plattner, U. S. pat. 2,429,171 [*C. A.*, **42**, 930 (1948)].

[5] Plattner and Geiger, *Helv. Chim. Acta*, **28**, 1362 (1945).

α-(4-CHLOROPHENYL)-γ-PHENYLACETOACETONITRILE

[Acetoacetonitrile, 2-(*p*-chlorophenyl)-4-phenyl-]

$$p\text{-ClC}_6\text{H}_4\text{CH}_2\text{CN} + \text{C}_6\text{H}_5\text{CH}_2\text{COOC}_2\text{H}_5 \xrightarrow{\text{NaOC}_2\text{H}_5} [p\text{-ClC}_6\text{H}_4\text{C(CN)COCH}_2\text{C}_6\text{H}_5]^{\ominus}\text{Na}^{\oplus}$$

$$[p\text{-ClC}_6\text{H}_4\text{C(CN)COCH}_2\text{C}_6\text{H}_5]^{\ominus}\text{Na}^{\oplus} + \text{HCl} \rightarrow p\text{-ClC}_6\text{H}_4\text{CH(CN)COCH}_2\text{C}_6\text{H}_5 + \text{NaCl}$$

Submitted by STEPHEN B. COAN and ERNEST I. BECKER.[1]
Checked by CHARLES C. PRICE and G. VENKAT RAO.

1. Procedure

A solution of 11.5 g. (0.5 g.-atom) of sodium is prepared in 150 ml. of absolute ethanol (Note 1) in a 500-ml. three-necked

flask equipped with a stirrer, a condenser, and a dropping funnel. While this solution is refluxing with stirring, a mixture of 37.8 g. (0.25 mole) of 4-chlorophenylacetonitrile and 50.8 g. (0.31 mole) of ethyl phenylacetate is added through the dropping funnel over a period of 1 hour. The solution is refluxed for 3 hours, cooled, and poured into 600 ml. of cold water. The aqueous alkaline mixture is extracted three times with 200-ml. portions of ether and the ether extracts discarded. The aqueous solution is acidified with cold 10% hydrochloric acid and extracted three times with 200-ml. portions of ether. The ether solution is then extracted once with 100 ml. of water, twice with 100 ml. each of 10% sodium bicarbonate solution, and once with 100 ml. of water, the aqueous extracts being discarded in turn. The organic phase is dried with anhydrous sodium sulfate, filtered through a fluted filter, and the ether removed by distillation. The yield of α-(4-chlorophenyl)-γ-phenylacetoacetonitrile is 58–62 g. (86–92%), m.p. 128.5–130.0°. For many purposes, this crude product may be used without further purification. If a purer product is desired, however, it may be recrystallized from methanol or aqueous methanol (Note 2) to yield 50–55 g. (74–82%), m.p. 131.0–131.2° (Note 3).

2. Notes

1. Comparable results were obtained when fresh commercial-grade (2-B) anhydrous ethanol was used.

2. For recrystallization, a solution of the nitrile in 3–4 ml. of hot methanol per gram was treated with Darco G-60 and filtered on a fluted paper. Distilled water was added to the hot solution until incipient crystallization was observed. In general the final solvent was approximately 90% methanol.

3. The above method has been used in the preparation of other ring-substituted diphenylacetoacetonitriles. The method is equally successful when applied to the condensation of phenylacetonitrile with the ethyl ester of a 4-substituted phenylacetic acid. The table summarizes the results reported by the submitters.

Diphenylacetoacetonitriles

Acetoacetonitrile	Yield, %	Melting Point, °C.
From phenylacetonitrile and an ethyl 4-substituted phenylacetate		
α-Phenyl-γ-phenyl-	82	79.4–80.0
α-Phenyl-γ-(4-methylphenyl)-	84	88.0–89.0
α-Phenyl-γ-(4-methoxyphenyl)-	81	69.5–70.4
α-Phenyl-γ-(4-bromophenyl)-	80	94.0–95.0
α-Phenyl-γ-(4-methylthiophenyl)-	85	85.0–85.2
From 4-substituted phenylacetonitrile and ethyl phenylacetate		
α-(4-Fluorophenyl)-γ-phenyl-	75	111.8–112.0

3. Methods of Preparation

The above procedure is a modification of that described by Walther and Hirschberg.[2] α,γ-Diphenylacetoacetonitrile has been prepared by the condensation of phenylacetonitrile with ethyl phenylacetate in the presence of sodium ethoxide without solvent.[3]

[1] Polytechnic Institute of Brooklyn, Brooklyn 2, New York.

[2] Walther and Hirschberg, *J. prakt. Chem.*, [2] **67**, 377 (1903).

[3] Walther and Schickler, *J. prakt. Chem.*, [2] **55**, 305 (1897).

1-(*p*-CHLOROPHENYL)-3-PHENYL-2-PROPANONE

[2-Propanone, 1-(*p*-chlorophenyl)-3-phenyl-]

$$p\text{-ClC}_6\text{H}_4\text{CH(CN)COCH}_2\text{C}_6\text{H}_5 \xrightarrow[\text{H}_2\text{SO}_4]{\text{H}_2\text{O}} p\text{-ClC}_6\text{H}_4\text{CH}_2\text{COCH}_2\text{C}_6\text{H}_5$$

Submitted by Stephen B. Coan and Ernest I. Becker.[1]
Checked by Charles C. Price and G. Venkat Rao.

1. Procedure

In a 250-ml. three-necked flask equipped with a stirrer and a condenser are placed 75 ml. of 60% sulfuric acid and 25 g. (0.093 mole) of α-(4-chlorophenyl)-γ-phenylacetoacetonitrile.[2] While being stirred, the mixture is heated at reflux until the evolution of carbon dioxide ceases (Notes 1 and 2). The mixture is cooled, poured into 200 ml. of ice water, and extracted three times with 150-ml. portions of ether. The ether solution is washed once with 50 ml. of water, twice with 100-ml. portions of 10% sodium hydroxide solution, and then with 50 ml. of water. After drying over sodium sulfate and filtering, the ether is distilled on a steam bath, affording 15–17 g. (66–75%) of 1-(*p*-chlorophenyl)-3-phenyl-2-propanone, m.p. 34.5–35.5°. Recrystallization from 160 ml. of petroleum ether (b.p. 40–60°) gives 12–13 g. (53–57%), m.p. 35.9–36.5° (Note 3).

2. Notes

1. The hydrolysis and decarboxylation of the nitrile require from 18 to 24 hours.
2. The evolution of carbon dioxide is conveniently observed by passing the effluent gases through a saturated solution of barium hydroxide.
3. The submitters report that a similar procedure has been used in the preparation of other monosubstituted dibenzyl ketones from α-phenyl-γ-(4-substituted phenyl)acetoacetonitriles.

Product	Yield, %	Melting Point, °C.
1,3-Diphenyl-2-propanone	65–71	34.2–34.5
1-(*p*-Tolyl)-3-phenyl-2-propanone	66	30.8–31.2
1-(*p*-Bromophenyl)-3-phenyl-2-propanone	50	53.8–54.2
1-(*p*-Fluorophenyl)-3-phenyl-2-propanone	50	36.0–36.5
1-(*p*-Methylthiophenyl)-3-phenyl-2-propanone	40	43.9–44.2
1-(*p*-Methoxyphenyl)-3-phenyl-2-propanone *	19	46.6–47.4

* It is necessary to employ 5 ml. of glacial acetic acid and 5 ml. of 20% aqueous hydrochloric acid, instead of the sulfuric acid, per gram of ketonitrile as reaction solvent in order to obtain the desired product.

3. Methods of Preparation

This method of preparation of 1-(*p*-chlorophenyl)-3-phenyl-2-propanone has been reported by Coan and Becker.[3] The method utilized is a modification of that described for the formation of 1,3-diphenyl-2-propanone from α,γ-diphenylacetoacetonitrile.[4, 5]

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[1] Polytechnic Institute of Brooklyn, Brooklyn 2, New York.

[2] *Org. Syntheses*, **35**, 30 (1955).

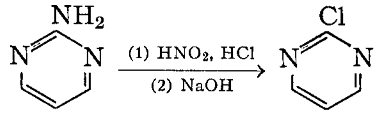
[3] Coan and Becker, *J. Am. Chem. Soc.*, **76**, 501 (1954).

[4] Meyer, *J. prakt. Chem.*, [2] **52**, 81 (1895).

[5] Walther and Schickler, *J. prakt. Chem.*, [2] **55**, 305 (1897).

2-CHLOROPYRIMIDINE

(Pyrimidine, 2-chloro-)



Submitted by Irving C. Kogon, Ronald Minin, and C. G. Overberger.[1]
Checked by Charles C. Price and T. L. V. Ulbricht.

1. Procedure

Caution! This procedure should be carried out in a good hood.

In a 3-l. three-necked round-bottomed flask fitted with a stirrer and a low-temperature thermometer is placed 500 ml. of concentrated hydrochloric acid (6.0 moles), and the solution is cooled to 0°. To the cooled solution, 142 g. (1.5 moles) of 2-aminopyrimidine (Note 1) is added portionwise with stirring until a homogeneous solution is obtained. The solution is cooled to −15° (Note 2), and a 500-ml. dropping funnel is fitted to the flask. A cold solution of 207 g. (3.0 moles) of sodium nitrite in 375 ml. of water is then added dropwise with stirring over a period of 55 minutes, the reaction temperature being maintained at −15° to −10° (Note 3). The solution is stirred an additional hour, and the temperature is allowed to rise to −5°. The mixture is then carefully neutralized to about *p*H 7 with a 30% solution of sodium hydroxide (about 3.0 moles), care being taken not to allow the temperature to rise above 0° (Note 4). The solid which forms, consisting of 2-chloropyrimidine and sodium chloride, is collected by filtration and washed thoroughly with ether to dissolve all the 2-chloropyrimidine. The cold solution is extracted with four 75-ml. portions of ether (Note 5). The combined extracts are dried over anhydrous sodium sulfate, the solvent is removed, and the residue is recrystallized from isopentane to give white crystals of 2-chloropyrimidine. The yield is 44–46 g. (26–27%), m.p. 64.5–65.5°.

2. Notes

1. Purchased from the Matheson, Coleman and Bell Company, Norwood, Ohio.
2. Cooling below −15° causes the mixture to solidify.
3. Care should be exercised since at this point nitrogen oxides are being evolved. Addition should be started cautiously, as there tends to be a rapid initial rise in temperature.
4. Yields are appreciably reduced if the temperature is allowed to rise above 0°.
5. Filtration and extraction should be performed immediately or extensive decomposition occurs.

3. Methods of Preparation

2-Chloropyrimidine has been prepared by a similar procedure by Howard.[2] The compound has also been prepared from 2-hydroxypyrimidine hydrochloride by treatment with a mixture of phosphorus pentachloride and phosphorus oxychloride[3] or by treatment with phosphorus oxychloride alone.[4]

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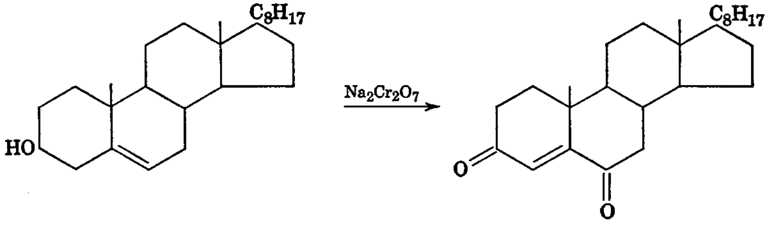
[1] Department of Chemistry, Polytechnic Institute of Brooklyn, Brooklyn 2, New York.

[2] Howard, U. S. pat. 2,477,409 [*C. A.*, **43**, 8105 (1949)].

[3] Matsukawa and Ohta, *J. Pharm. Soc. Japan.*, **69**, 491 (1949) [*C. A.*, **44**, 3456 (1950)].

[4] Copenhaver and Kleinschmidt, Brit. pat. 663,302 [*C. A.*, **46**, 10212 (1952)].

Δ^4-CHOLESTEN-3,6-DIONE



Submitted by Louis F. Fieser.[1]
Checked by William S. Johnson and David G. Martin.

1. Procedure

A 500-ml. Erlenmeyer flask containing 64 g. (10 oxygen equivalents) of sodium dichromate dihydrate and 225 ml. of acetic acid is heated and swirled until all the solid has dissolved, and then is cooled in an ice bath to bring the temperature of the solution to 15°. In a 1-l. Erlenmeyer flask 25 g. (0.065 mole) of commercial cholesterol is dissolved in 225 ml. of benzene by brief warming, and the solution is cooled to 20°; 225 ml. of acetic acid is added, the solution is cooled to 15°, and the dichromate solution (at 15°) is poured in, whereupon a thick orange paste of cholesteryl chromate, $(C_{27}H_{45}O)_2CrO_2$, separates. The flask is immersed in an ice-water bath that is allowed to stand in a refrigerator for 40–48 hours. No stirring or other attention is required in this period; the temperature soon drops to 0° (Note 1), and the chromate dissolves in a few hours.

The resulting brown solution is poured into a separatory funnel and shaken with 225 ml. of 30–60° petroleum ether. After brief standing, the mixture when viewed against a strong light can be seen to have separated into a reddish upper hydrocarbon layer and a smaller, very dark lower layer containing chromium compounds and acetic acid. The lower layer is drawn off and discarded. Then 50 ml. of water is added to the hydrocarbon layer, and the mixture is shaken and allowed to settle. A further lighter-colored, lower layer is drawn off and discarded, and the process is repeated with 50 ml. more water. The hydrocarbon layer, now light in color, is then shaken with 110 ml. of Claisen's alkali (Note 2); this first portion neutralizes the residual acetic acid and acidic oxidation products, and extracts some of the enedione as the yellow enolate. The funnel is allowed to stand, with occasional twirling, until the lower layer has settled to a clear yellow solution; the upper hydrocarbon layer acquires a dirty red-brown color. The extract is drawn off into a wide-mouthed 2-l. separatory funnel charged with 200 ml. of water, 600 g. of ice, 200 ml. of 36% hydrochloric acid, and 300 ml. of ether (Note 3). The hydrocarbon layer is extracted in the same way with five more 100-ml. portions of Claisen's alkali and then discarded (Note 4).

After the last alkaline extract has been run into the receiving funnel, this is shaken and the aqueous layer is drawn off and discarded. The light-yellow ethereal layer is run into a smaller funnel and shaken with 100 ml. of 5% sodium carbonate solution and 30 ml. of saturated sodium chloride solution (Note 5). This extraction is repeated a second time (Note 6). The carbonate extract is either discarded or worked up for recovery of acidic oxidation products (Note 7). The ethereal solution is finally shaken with 100 ml. of saturated sodium chloride solution, filtered into a round-bottomed flask (Note 8) by gravity through a paper containing 25 g. of anhydrous magnesium sulfate, and evaporated to dryness. The residue is initially an oil, but when the last traces of solvent are removed by evacuating the flask (Note 8), reheating, and re-evacuating, it is obtained as a yellow solid (about 13 g.). This is taken up in 125 ml. of boiling methanol, and crystallization is allowed to proceed, first at room temperature and then at 0°. Δ^4-Cholesten-3,6-dione separates in glistening, thin, yellow plates, m.p. 124–125°; yield in the first crop, 9.0–9.3 g. Concentration of the filtrate affords a second crop of 0.7–1.2 g., melting in the range 118–121.5°; total yield, 10.0–10.2 g. (39–40%).

2. Notes

1. The temperature of the oxidation is highly critical. When the mixture, initially at 15°, is allowed to stand in a refrigerator at an air temperature of 4–8°, the temperature of the reaction mixture during the first 7 hours is in the range 18–5° (exothermic); yields of enedione after varying reaction periods are as follows: 7 hours, 27%; 15–22 hours, 32.5% (less-pure product). At 25° the enedione is oxidized completely to acids in about 18 hours.

2. Sufficient Claisen's alkali for one run is made by dissolving 175 g. of potassium hydroxide pellets in 125 ml. of distilled water, cooling to room temperature, adding 500 ml. of methanol, and again cooling; this gives 655–665 ml. of solution.

3. Δ^4-Cholesten-3,6-dione is sensitive to air oxidation under certain conditions, particularly in alkaline solution. If the protective procedure specified is not followed the reaction product may be deep red and tarry.

4. The residual solution contains a little cholesterol, 0.2–0.3 g. of Δ^4-cholesten-3,6-dione, and small amounts of products derived from the oxidation of cholestanol and other companions.

5. Sodium chloride speeds up the separation of layers.

6. The sodium carbonate extract contains only a few milligrams of the enedione.

7. The oxidation procedure described affords a mixture of acids from which no component is easily isolable. When the oxidation is allowed to proceed in the temperature range 18-5° for 15–22 hours, as described in Note 1, isolation of the Diels acid (3,4-seco-Δ^5-cholesten-3,4-dioic acid) is easily accomplished as follows. The carbonate extract is acidified and shaken with ether, and the clear aqueous layer is discarded. The ethereal solution, which may contain some suspended Diels acid, is not dried but is run into a flask and diluted with an equal volume of acetone. The mixture is evaporated to a volume of 15–20 ml. and cooled, and the Diels acid is collected as a white powder, m.p. 280–285°; yield 0.5 g.

8. A round-bottomed flask is recommended in order to withstand the evacuation process.

3. Methods of Preparation

Mauthner and Suida[2] isolated, as one of three neutral products resulting from the oxidation of cholesterol with aqueous chromic acid in acetic acid solution, the substance later identified as Δ^4-cholesten-3,6-dione. The present procedure is based upon results of a reinvestigation of the oxidation by a low-temperature, non-aqueous procedure.[3]

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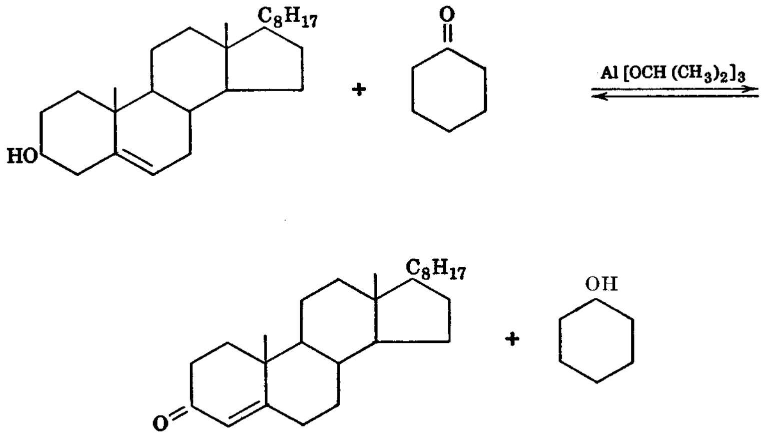
[1] Department of Chemistry, Harvard University, Cambridge 38, Massachusetts.

[2] Mauthner and Suida, *Monatsch.*, **17**, 579 (1896); see also Windaus, *Ber.*, **39**, 2249 (1906); Ross, *J. Chem. Soc.*, **1946**, 737.

[3] Fieser, *J. Am. Chem. Soc.*, **75**, 4386 (1953).

Δ^4-CHOLESTEN-3-ONE



Submitted by Jerome F. Eastham and Roy Teranishi.[1]
Checked by James Cason, James Jiu, and Elmer J. Reist.

1. Procedure

To a 5-l. three-necked flask, equipped with a sealed mechanical stirrer, a dropping funnel, and a take-off reflux condenser, are added 2 l. of sulfur-free toluene and two boiling chips. The openings of the dropping funnel and the condenser are protected by drying tubes containing Drierite. A portion (200 ml.) of the toluene is distilled from the flask (take-off cock open) in order to dry the system by azeotropic distillation; then 100 g. (0.31 mole) of cholesterol and 500 ml. of cyclohexanone (Note 1) are added to the flask. After an additional 50 ml. of toluene has been distilled, a solution of 28 g. (0.18 mole) of aluminum isopropoxide (Note 2) in 400 ml. of dry toluene (Note 3) is added dropwise over a period of approximately 30 minutes. During this time toluene is distilled at a rate slightly greater than the rate of addition of catalyst solution, so that when the addition is complete about 600 ml. of toluene has distilled. An additional 300 ml. of toluene is distilled, and the murky orange-colored reaction mixture is then allowed to cool to room temperature.

Four hundred milliliters of a saturated aqueous solution of potassium-sodium tartrate (Note 4) is added to the mixture, and the organic layer becomes clear and orange. The stirrer assembly is removed, and the mixture is steam-distilled until about 6 l. of distillate has been collected. The residual mixture is cooled and extracted successively with one 300-ml. portion and two 100-ml. portions of chloroform. The combined extracts are washed with two 100-ml. portions of water and dried over anhydrous magnesium sulfate. The chloroform is removed by distillation on the steam bath at reduced pressure (water aspirator). The residual viscous amber oil (Note 5) is dissolved by heating in 150 ml. of methanol. When the solution has cooled to about 40°, seeds of cholestenone are added, and the flask is wrapped with a small towel to ensure slow cooling (Note 6). After the bulk of the material has crystallized, which requires several hours, the mixture is stored at 0° overnight (Note 7). The product is collected by suction filtration, washed with 40–50 ml. of methanol previously cooled in an ice-salt bath, then dried at reduced pressure, first at room temperature and finally at 60°. The yield of light-cream-colored Δ^4-cholesten-3-one is 81–93 g. (81–93%), m.p. 76–79°. Recrystallization from methanol gives material melting at 79.5–80.5° in 90% recovery (Note 8).

2. Notes

1. Commercial cholesterol, m.p. 146–149°, is satisfactory if dried at reduced pressure at 100° for 48 hours. The cyclohexanone is simply distilled before use, b.p. 153–155°.

2. Directions for the preparation of aluminum isopropoxide are given by Young, Hartung, and Crossley.[2] This compound is also commercially available. Turbidity of the catalyst solution is to be expected and is not detrimental.

3. Toluene is dried satisfactorily by distilling about 20% of it and using the residue, which is cooled with protection from moisture.

4. Either Rochelle or Seignette salt is satisfactory. The tartrate ion serves to keep the aluminum ion in solution.

5. Prolonged heating is not necessary, since the chloroform remaining with the residual oil does not hamper the crystallization.

6. Seed crystals may be obtained by transferring a few drops of the solution to a small test tube, then cooling and scratching.

Ordinarily the cholestenone will separate as an oil from a solution saturated much above 50°. In this event, rather than working with larger volumes of methanol, small portions of chloroform may be added to the solution to lower the saturation temperature to a point at which seed crystals do not turn to oil. The best yield of good crystalline product is realized by inducing crystallization at the highest possible temperature in order to obtain a large initial crop of crystals. A second crop is difficult if not impossible to obtain by direct crystallization.

The towel should be placed around the flask only after crystallization, rather than oil formation, is assured. The towel is carefully removed occasionally during the first hour to ascertain whether oil is forming on top of the crystals. If so, the solution is warmed slightly in order to redissolve the oil but not the crystals. The product is quite impure if it first separates as an oil which later crystallizes.

7. If initial crystallization is not induced at 40° or above, a further period of cooling in an ice-salt bath is necessary to obtain the best yield.

8. In order to avoid large volumes, it is recommended that 700 ml. of methanol be employed to recrystallize 90 g. of cholestenone and that either chloroform or acetone be used to increase the solubility of the cholestenone to the required amount.

3. Methods of Preparation

Methods of preparation of Δ^4-cholesten-3-one have been summarized in an earlier volume.[3] The present modification is less laborious than the earlier method.

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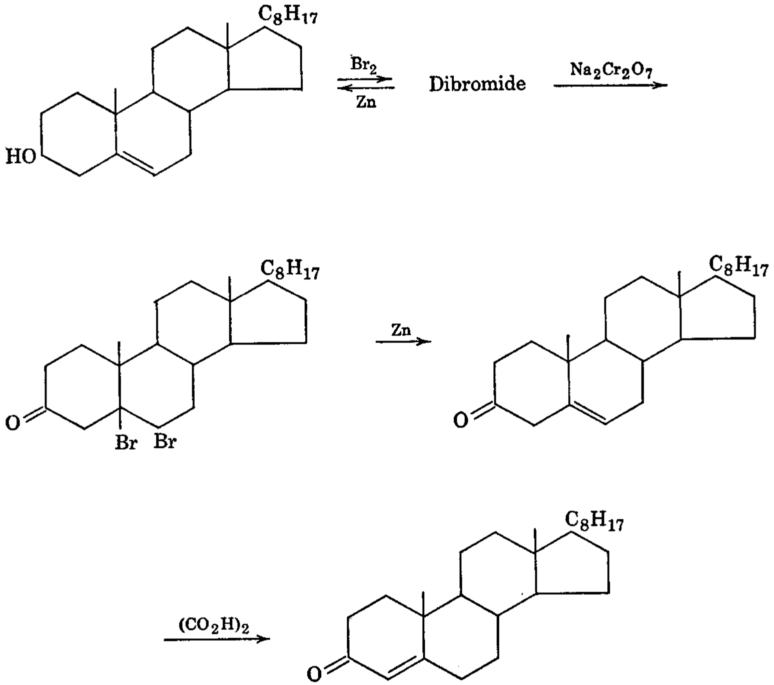
[1] Department of Chemistry and Chemical Engineering, University of California, Berkeley, California.

[2] Young, Hartung, and Crossley, *J. Am. Chem. Soc.*, **58**, 100 (1936).

[3] *Org. Syntheses* Coll. Vol. **3**, 207 (1955).

CHOLESTEROL, Δ^5-CHOLESTEN-3-ONE, AND Δ^4-CHOLESTEN-3-ONE



Submitted by Louis F. Fieser.[1]
Checked by William S. Johnson and David G. Martin.

1. Procedure

A. *Cholesterol dibromide.* In a 4-l. beaker 150 g. (0.39 mole) of commercial cholesterol (Note 1) is dissolved in 1 l. of absolute ether by warming on the steam bath and stirring with a stout glass rod; the solution is then cooled to 25°. A second solution is prepared by adding 5 g. of powdered anhydrous sodium acetate (0.06 mole) (Note 2) to 600 ml. of acetic acid, stirring the mixture and breaking up the lumps with a flat stirring rod; 68 g. (0.4 mole) of bromine is then added, and the solution is poured with stirring into the cholesterol solution. The solution turns yellow and promptly sets to a stiff paste of dibromide. The mixture is cooled in an ice bath to 20°, and then the product is collected on a 16-cm. Büchner funnel (Note 3). The cake is pressed down and washed with acetic acid until the filtrate is completely colorless; 500 ml. is usually sufficient. A second crop of satisfactory dibromide is obtained by adding 800 ml. of water to the combined filtrate and washings, collecting the precipitate, and washing it with acetic acid until colorless. Dibromide moist with acetic acid is satisfactory for most transformations; dry dibromide, even when highly purified by repeated crystallization, begins to decompose (darkens) within a few weeks. When material prepared as described is dried to constant weight at room temperature, it is obtained as the 1:1 dibromide/acetic acid complex. Yields obtained in the first and second crops, respectively, are: 171–186 g. and 13–25 g., total yield 197–199 g. (84–85%) (Note 1).

B. *Cholesterol from the dibromide.* The acetic acid-moist filter cake of dibromide from 150 g. of cholesterol is transferred (Note 3) to a 3-l. round-bottomed flask and covered with 1.2 l. of U.S.P. ether, and the suspension is stirred mechanically above a bucket of ice and water that can be raised as required (Notes 4, 5). Forty grams (0.61 gram atom) of fresh zinc dust is added in the course of 5 minutes. The first 5- to 10-g. portion is added without cooling; when the reaction has started, as evidenced by solution of part of the dibromide and by ebullition, the cooling bath is raised during the remainder of the addition. At the end, the ice bath is lowered, and the mixture, which soon sets to a paste of white solid (Note 6), is stirred for 15 minutes longer. Then 50 ml. of water is added to dissolve the white solid, and the ethereal solution is decanted into a separatory funnel and washed with 400 ml. of water containing 25 ml. of 36% hydrochloric acid. After three more washings with 400-ml. portions of water, the solution is shaken thoroughly with 300 ml. of water and 150 ml. of 25% sodium hydroxide solution, and the ethereal solution is tested with moist blue litmus paper to make sure that all the acetic acid is removed (Note 7). The solution is then dried over magnesium sulfate and evaporated to a volume of 600 ml., methanol (600 ml.) is added, and the solution is evaporated to the point where crystallization just begins (about 1 l.). After standing at room temperature and then at 0–4°, the main crop of cholesterol is collected and dried at room temperature; yield 108–110 g., m.p. 149.5–150° (Note 8). A second crop of 8.4–10.4 g., m.p. 148–149°, is obtained after evaporation of the mother liquor to a volume of 250 ml. (Note 9); total yield 117–120 g. (78–80% from commercial cholesterol) (Note 10).

C. *5α,6β-Dibromocholestan-3-one.* The moist dibromide from 150 g. of cholesterol (part A) is suspended in 2 l. of acetic acid in a 5-l. round-bottomed flask equipped with a stirrer and mounted over a bucket of ice and water that later can be raised to immerse the flask (Note 5). The suspension is stirred at room temperature (25–30°), and a solution, preheated to 90°, of 80 g. (2 oxygen equivalents) of sodium dichromate dihydrate in 2 l. of acetic acid is poured in through a funnel (Note 3). The mixture reaches a temperature of 55–58° during the oxidation, and all the solid dissolves in 3–5 minutes. After another 2 minutes the ice bucket is raised until the flask is immersed; stirring is then stopped, and the mixture is allowed to stand in the ice bath without disturbance for 10 minutes to allow the dibromoketone to separate in easily filterable crystals. With stirring resumed, the temperature is brought to 25° and then, after addition of 400 ml. of water, to 15°. The product is collected on a 21-cm. Büchner funnel, and the filter cake is drained until the flow of filtrate amounts to no more than 25 drops per minute. The suction is released, the walls of the funnel are washed down with methanol, and 200 ml. of methanol is added. After a few minutes' standing, suction is applied and the crystals are drained thoroughly of solvent before they are washed in the same way with 200 ml. of fresh methanol. The last drops of filtrate should be completely colorless. Dried to constant weight at room temperature in a dark cupboard, the dibromoketone consists of shiny white crystals, m.p. 73–75° (dec.), $[\alpha]^{25}_{D}$ −47° chloroform ($c = 2.11$) (Note 11); yield about 171 g. (96% in the oxidation or 81% from cholesterol).

D. Δ^5-*Cholesten-3-one.* (Note 12.) The moist 5α,6β-dibromocholestan-3-one from 150 g. of cholesterol is transferred to a 3-l.

round-bottomed flask and covered with 2 l. of U.S.P. ether and 25 ml. of acetic acid. The suspension is stirred mechanically, an ice bath is raised into position (Note 5), and the temperature is brought to 15°. The ice bath is then lowered, and 5 g. of fresh zinc dust is added. As soon as the exothermic reaction of debromination sets in, the temperature is controlled to 15–20° by cooling during the addition (in about 5 minutes) of 35 g. more zinc dust. The ice bath is then lowered, and the ethereal solution containing suspended zinc dust is stirred for 10 minutes longer. With continued stirring, 40 ml. of pyridine is added; this precipitates a white zinc salt (Note 13). The mixture is filtered through a Büchner funnel, and the filter cake is washed well with ether. The colorless filtrate is washed with three 600-ml. portions of water and then shaken thoroughly with 600 ml. of 5% aqueous sodium bicarbonate solution until free from acetic acid as indicated by testing the ethereal solution with moist blue litmus paper. The solution is dried over magnesium sulfate and evaporated to a volume of about 1 l.; 500 ml. of methanol is added, and the evaporation is continued until the volume is approximately 1.2 l. Crystallization is allowed to proceed at room temperature, then at 0–4°, and the large colorless prisms are collected by suction filtration; yield in the first crop 87–94 g., melting point in the range 124–129° (camphorlike odor), $[\alpha]^{25}_{D}$ −2.5° chloroform ($c = 2.03$), no selective absorption at 242 mμ. Concentration of the mother liquor gives a second crop of 12–19 g. melting in the range 117–125° and suitable for conversion to Δ^4-cholesten-3-one; total yield 106–108 g. (71–72% from cholesterol).

E. *Δ^4-Cholesten-3-one.* A mixture of 100 g. of Δ^5-cholesten-3-one (0.26 mole), 10 g. (0.11 mole) of anhydrous oxalic acid (Note 14), and 800 ml. of 95% ethanol is heated on the steam bath until all the solid is dissolved (15 minutes) and for 10 minutes longer, and then is allowed to stand at room temperature. If crystallization has not started after a period of several hours, the solution is seeded or scratched. After crystallization has proceeded at room temperature and then at 0–4°, the large, colorless, prismatic needles that separate are collected by suction filtration; yield in the first crop 88–92 g., m.p. 81–82°, $[\alpha]^{25}_{D}$ 92° chloroform ($c = 2.01$); $\lambda^{\text{ethanol}}_{\text{max.}}$ 242 mμ ($\epsilon = 17{,}000$). A second crop (5.0–7.5 g., melting in the range 78–82°) is obtained after concentration of the mother liquor to a volume of about 100 ml., and a third crop (3–4 g., low melting) by dilution with water. Recrystallization of these crops from 95% ethanol gives a total of 6.8–8.1 g. of satisfactory material, m.p. 81–82°; total yield 96–98 g. (68–69% over-all yield from cholesterol).

2. Notes

1. Cholesterol of high quality and of recent production was employed. Cholesterol undergoes slow autoxidation in the solid state, and samples that have been in storage for a few years give lower yields of dibromide. The checkers used U.S.P. material, m.p. 149–150°, as supplied by Wilson Company, Chicago, Illinois.

2. The yield of dibromide dropped from 84% to 73% when no buffering sodium acetate was used. No improvement resulted from doubling the quantity of sodium acetate specified. Buffered bromination in a stirred suspension of acetic acid (no ether) at 20° raised the yield to 89%, but this material on debromination afforded sterol of low melting point (145–147°) containing halogen (Beilstein test).

3. The operation should be done in a hood, and the hands should be protected with Neoprene gloves.

4. If dry dibromide is used, 25 ml. of acetic acid is added to the suspension.

5. The ice bucket is conveniently mounted on an automobile jack.

6. The solid appears to be a complex of cholesterol and a zinc salt.

7. If the acetic acid is not removed some cholesteryl acetate may be formed during the evaporation.

8. The melting-point determination should be done in an evacuated capillary tube. In an open tube autoxidation occurs readily enough to lower the melting point when the bath is heated very slowly.

9. The residual mother liquor contains about 4 g. of material

containing bromine not removed by repetition of the treatment with zinc dust.

10. Purification of cholesterol through the dibromide completely eliminates cholestanol, 7-dehydrocholesterol, and lathosterol (Δ^7-cholestenol). The first crop of material from methanol-ether is also free from cerebrosterol (24-hydroxycholesterol) and 25-hydroxycholesterol, a product of autoxidation present in cholesterol that has been stored in the crystalline state for a few years with access to air. When material of highest purity is desired, only first-crop dibromide should be employed, since debromination of second-crop material gives sterol melting at 146–147° and giving a positive Beilstein test.

11. Dibromocholestanone sometimes begins to decompose (turns purplish) after standing in the dark for a few hours; it rapidly darkens when dried at 70° or when exposed to bright sunlight. Hence it is advisable to use the material moist with methanol directly after preparation.

12. For success in the preparation of this labile non-conjugated ketone in high yield and purity, the intermediates, cholesterol dibromide and dibromocholestanone, should be processed further in the solvent-moist state as soon as prepared. The three reactions can be completed easily in one day.

13. If the bulk of the ionic zinc is not precipitated at this point it will cause troublesome emulsions when the solution is washed with water.

14. When isomerization of 100-g. batches of non-conjugated ketone was effected in ethanol under catalysis by either hydrochloric acid or sodium hydroxide (followed by neutralization of the yellow enolate solution with acetic acid), a permanent yellow coloration developed, the first-crop material was yellowish and melted at 78–80°, and the second-crop material was very impure.

3. Methods of Preparation

Cholesterol dibromide has been prepared by unbuffered [2] and buffered [3] bromination of cholesterol and oxidized to 5α,6β-dibromocholestan-3-one with acid permanganate,[2] chromic acid,[4, 5, 6] and sodium dichromate.[3] Regeneration of sterols, or more usually of sterol acetates, from their dibromides has been accomplished by use of zinc dust in boiling acetic acid,[2] sodium iodide,[7] ferrous chloride,[8] and chromous chloride,[9] and by the method [3] here described. Δ^5-Cholesten-3-one has been prepared by debromination of dibromocholestanone with zinc dust in boiling ethanol or methanol [5] and by zinc dust in ether containing a little acetic acid.[3]

The Oppenauer oxidation of cholesterol to Δ^4-cholesten-3-one of m.p. 77–79° in 70–93% yield has been reported in these volumes.[10] Isomerization of Δ^5-cholesten-3-one by a mineral acid or a base has been conducted satisfactorily only on a micro scale; [5] the method of isomerization with oxalic acid has been reported.[3]

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[1] Department of Chemistry, Harvard University, Cambridge 38, Massachusetts.

[2] Windaus, *Ber.*, **39**, 518 (1906).

[3] Fieser, *J. Am. Chem. Soc.*, **75**, 5421 (1953).

[4] Ruzicka, Brungger, Eichenberger, and Meyer, *Helv. Chim. Acta*, **17**, 1413 (1934).

[5] Butenandt and Schmidt-Thome, *Ber.*, **69**, 882 (1936).

[6] Inhoffen, *Ber.*, **69**, 1134 (1936).

[7] Schoenheimer, *Z. physiol. Chem.*, **192**, 86 (1930); *J. Biol. Chem.*, **110**, 461 (1935).

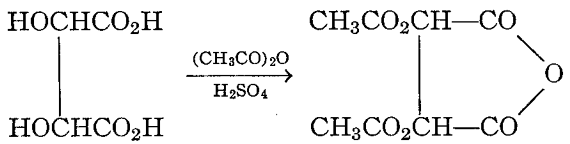
[8] Bretschneider and Ajtai, *Monatsh.*, **74**, 57 (1943).

[9] Julian, Cole, Magnani, and Meyer, *J. Am. Chem. Soc.*, **67**, 1728 (1945).

[10] *Org. Syntheses* Coll. Vol. **3**, 207 (1955); *Organic Syntheses*, **35**, 39 (1955).

DIACETYL-*d*-TARTARIC ANHYDRIDE

(Tartaric anhydride, diacetate of *d*-)



Submitted by R. L. Shriner and C. L. Furrow, Jr.[1]
Checked by N. J. Leonard and R. R. Sauers.

1. Procedure

In a 500-ml. three-necked round-bottomed flask fitted with a liquid-sealed stirrer and two reflux condensers (Note 1) is placed

40 g. (0.27 mole) of anhydrous, powdered *d*-tartaric acid (Note 2). A solution of 1.2 ml. of concentrated sulfuric acid in 136 g. (126 ml., 1.33 moles) of acetic anhydride is added, and the stirrer is started. The mixture warms up, and the tartaric acid goes into solution. The solution is heated gently (Note 1) under reflux with stirring for 10 minutes. The solution is poured into a beaker and cooled for 1 hour in an ice bath. The crude crystalline product is collected on a 15-cm. Büchner funnel (Note 3), washed twice with 20-ml. portions of dry benzene, stirred mechanically with 175 ml. of cold absolute ether, filtered, and placed in a vacuum desiccator over phosphorus pentoxide and paraffin shavings for 24 hours. The yield of diacetyl-*d*-tartaric anhydride is 41–44.5 g. (71–77%), m.p. 133–134° (Note 4), $[\alpha]_{\mathrm{D}}^{20}$ 97.2° in dry chloroform ($c = 0.47$).

2. Notes

1. The reaction may be quite vigorous at its start, and the use of a large flask with two condensers is advised.

2. The anhydrous *d*-tartaric acid was obtained from Matheson, Coleman and Bell, East Rutherford, New Jersey.

3. Additional but lower-grade product may be acquired by pouring the mother liquor into petroleum ether and filtering the mixture. The recovered product is washed twice with absolute ether, filtered, and dried. About 7 g. of product, m.p. 129–131°, is thus obtained.

4. The product is not stable and should be prepared only as needed. It may be kept in a vacuum desiccator over phosphorus pentoxide and paraffin, but the melting point drops about 1 degree during the first 4 days and then remains constant at approximately 132–134°. If placed in an ordinary stoppered bottle, the product becomes gummy and the melting point falls to about 100° within 3 days. Attempts to recrystallize the anhydride invariably led to decomposition and lowered melting point.

3. Methods of Preparation

The acetylation of *d*-tartaric acid with acetic anhydride has been effected by means of sulfuric acid [2,3] or hydrogen chloride.[4]

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[1] Department of Chemistry, State University of Iowa, Iowa City, Iowa.

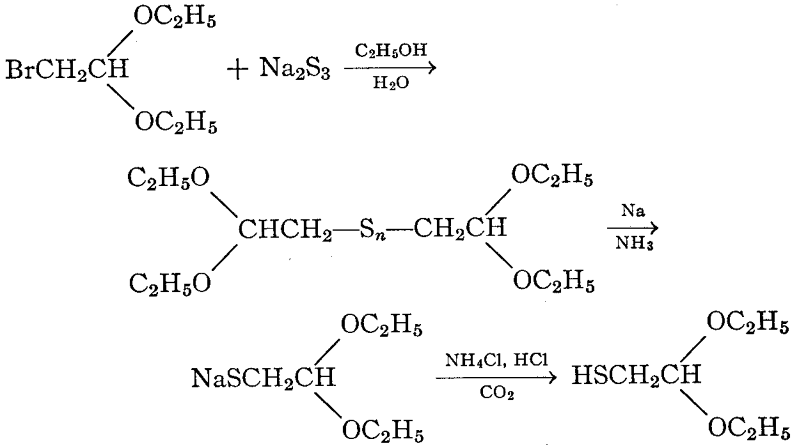
[2] Chattaway and Parkes, *J. Chem. Soc.*, **123**, 663 (1923).

[3] Roberts, *J. Chem. Soc.*, **1952**, 3315.

[4] Lucas and Baumgarten, *J. Am. Chem. Soc.*, **63**, 1653 (1941).

DIETHYL MERCAPTOACETAL

(Mercaptoacetaldehyde, diethyl acetal)



$$BrCH_2CH(OC_2H_5)_2 + Na_2S_3 \xrightarrow[H_2O]{C_2H_5OH} (C_2H_5O)_2CHCH_2{-}S_n{-}CH_2CH(OC_2H_5)_2 \xrightarrow[NH_3]{Na}$$

$$NaSCH_2CH(OC_2H_5)_2 \xrightarrow[CO_2]{NH_4Cl,\ HCl} HSCH_2CH(OC_2H_5)_2$$

Submitted by William E. Parham and Hans Wynberg.[1]
Checked by Max Tishler and George Purdue.

1. Procedure

A. *1,1,1′,1′-Tetraethoxyethyl polysulfide.* (Note 1.) In a 5-l. round-bottomed flask, equipped with a stirrer, a reflux condenser, and an addition funnel, 540 g. (2.25 moles) of sodium sulfide enneahydrate (Note 2) is dissolved in 2.7 l. of boiling 95% ethanol. Sulfur (144 g., 4.5 gram atoms) is added, and the solution is heated under reflux until it has assumed a deep red color (10 minutes). The source of heat is removed, and 588 g. (3 moles) of diethyl bromoacetal (Note 3) is added over a period of about 30 minutes at such a rate that the solution boils gently. The mixture is heated under reflux for an additional 4 hours. During the last hour of heating, ethanol is allowed to distil from the reaction flask, and after the first 700 ml. of distillate is collected sodium bicarbonate (135 g.) (Note 4) is added to the reaction mixture. A total of 2.0–2.5 l. of ethanol is collected. Water (1.5 l.) is added, and the upper layer is separated. The aqueous layer is extracted with two 250-ml. portions of ether, and the combined organic layers are washed successively with two 100-ml. portions of 10% sodium hydroxide solution, three 100-ml. portions of water, and two 250-ml. portions of saturated sodium chloride solution, and are dried over potassium carbonate. The ether is removed by distillation, and the residue is brought to constant weight by heating for about 1 hour on the steam bath at 10–15 mm. pressure. The orange liquid obtained in this way (Note 5) weighs 450–500 g. and has n_D^{25} 1.515–1.517.

B. *Diethyl mercaptoacetal.* A 12-l. three-necked flask, equipped with an efficient Hershberg stirrer, a Dry Ice condenser, and a stopper, is placed in an enameled container (Note 6). The flask is charged with 500 g. (1.38 moles, calculated as tetrasulfide) of 1,1,1′,1′-tetraethoxyethyl polysulfide and 500 ml. of anhydrous ether. The condenser is filled with acetone and Dry Ice, and the contents of the flask are cooled by means of acetone and Dry Ice kept at −35° to −45°. Liquid ammonia (Note 7) is introduced into the stirred solution until 4.5–5.0 l. has been added (Note 8). The solution is stirred for several minutes to ensure homogeneity, and 200 g. (8.7 gram atoms) of sodium is added in 2- to 5-g. lumps to the mixture over a period of 30–45 minutes. The last 2–10 g. of sodium causes the solution to turn deep blue. The mixture is stirred for 30 additional minutes, and ammonium chloride (about 200 g.) is cautiously added with stirring until the blue color is discharged. The cooling bath is removed and replaced by a bath of hot water into which steam may be introduced. The mixture is stirred while the ammonia is removed by distillation or evaporation (the distillation should be continued until the residue can no longer be stirred or is difficult to stir). The soft, semisolid mass containing small amounts of ammonia is cooled in ice, and 1 l. of ice-cold water is added with stirring. When most of the solid has dissolved, ice-cold hydrochloric acid is added cautiously, with frequent checks of the *p*H, until a *p*H of 8.0–8.5 is reached. The *p*H is then adjusted to 7.8–8.0 (preferably by a *p*H meter) by passing carbon dioxide into the cold solution (Note 9). The oil is separated from the aqueous layer, which is extracted with two 300-ml. portions of ether. The combined organic layers are washed successively with 100 ml. of water and two 100-ml. portions of saturated sodium chloride, and are dried over magnesium sulfate. The ether is removed by distillation, and the residue is distilled from a 500-ml. flask using a small Vigreux column or a Claisen head. The product (Note 10) weighs 320–372 g. (77–90% yield, based on polysulfide; 71–83% yield, based on bromoacetal), boils at 62–64°/12 mm., and has n_D^{25} 1.4391–1.4400. The residue, 23–27 g., n_D^{25} 1.4702–1.4730, consists mainly of 1,1,1′,1′-tetraethoxyethyl sulfide.

2. Notes

1. These directions have been used equally successfully with twice, one-third, and one-fifth the amounts specified. The reaction of chloro- or bromoacetal with sodium disulfide results in the formation of a considerable quantity of the corresponding monosulfide which is not subsequently reduced to mercaptan. Polysulfides are, however, easily reduced to mercaptans. 1,1,1′,1′-Tetramethoxyethyl polysulfide has been prepared from commercially available dimethyl chloroacetal in a similar fashion. A 10-hour heating period and the addition of 5 g. of potassium iodide per 100 g. of acetal are recommended in the latter preparation.

2. The sodium sulfide ($Na_2S \cdot 9H_2O$) should be crystalline and finely divided.

3. The procedure used for the preparation of diethyl bromoacetal (b.p. 78–79°/24 mm., n_D^{20} 1.4418) is that of Bedoukian.[2]

4. Di- and polysulfides are cleaved by strong alkali. The bicarbonate is added as a buffer.

5. Analysis of this material showed it to have the average composition calculated for a tetrasulfide; the yield of product, calculated as tetrasulfide, is 83–92%.

6. In order to use as little coolant as possible the flask should fit the container snugly.

7. All normal precautions should be observed during the handling of these large quantities of ammonia and sodium. A well-ventilated hood, a gas mask, and a bucket of sand were available to the submitters. The only hazard in this reaction may arise if too much ammonia escapes and the sodium does not react properly as a consequence. The addition of 0.5–1.0 l. of ammonia to the reaction mixture after the sodium has been added is a useful precaution.

8. The submitters measured the liquid ammonia in a 1-l. graduated cylinder.

9. Complete neutralization of the salt of mercaptoacetal with mineral acid may result in hydrolysis of the acetal.

10. Mercaptoacetal is sensitive to acid and oxygen. The product should be stored in a dry, alkali-washed bottle under nitrogen in a refrigerator.

3. Methods of Preparation

Diethyl mercaptoacetal has been prepared by treating diethyl bromoacetal with potassium hydrosulfide;[3] by the reduction of 1,1,1′,1′-tetraethoxyethyl disulfide[3] with lithium aluminum hydride; by reduction of 1,1-diethoxyethyl benzyl sulfide,[3,4] 1,1,1′,1′-tetraethoxyethyl disulfide,[3] and 1,1,1′,1′-tetraethoxyethyl polysulfide[3] with sodium and liquid ammonia. The method described is adapted from the last-named preparation. Dimethyl mercaptoacetal has been prepared by the same methods.[3]

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[1] Department of Chemistry, University of Minnesota, Minneapolis, Minnesota.

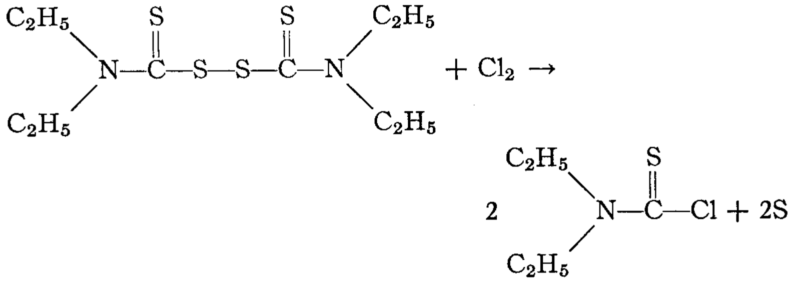
[2] Bedoukian, *J. Am. Chem. Soc.*, **66**, 651 (1944).

[3] Parham, Wynberg, and Ramp, *J. Am. Chem. Soc.*, **75**, 2065 (1953).

[4] Hesse and Jorder, *Ber.*, **85**, 924 (1952).

DIETHYLTHIOCARBAMYL CHLORIDE

(Carbamyl chloride, diethylthio-)



Submitted by R. H. Goshorn, W. W. Levis, Jr., E. Jaul, and E. J. Ritter.[1]
Checked by T. L. Cairns and H. E. Cupery.

1. Procedure

A 200-ml. three-necked flask, equipped with a mechanical stirrer arranged to permit escape of gas, a thermometer, and a gas-inlet tube 10 mm. in diameter (Note 1), is placed in a vessel to which cooling water may be added. The entire apparatus is placed in a well-ventilated hood (Note 2). The flask is charged with 74 g. (0.25 mole) of dry (Note 3), molten (70°) tetraethylthiuram disulfide (Note 4). The molten mass is stirred vigorously, and chlorine is passed through a safety trap and is introduced below the surface of the liquid through the inlet tube. The reaction is exothermic, and the temperature is held at 70–75° by adjusting the rate of chlorine addition and by surrounding the reaction flask with cold water. After approximately 6 g. of chlorine has been absorbed, the temperature is lowered to 50–55° and held in this range for the remainder of the chlorination (Note 5). When about 90% of the theoretical amount of chlorine has been added, sulfur begins to precipitate and the reaction mass changes from a clear yellow-to-red solution to a cloudy yellow mixture. The reaction is considered complete when 18 g. (0.254

mole) of chlorine has been absorbed (measured by gain in weight of the reaction mixture). The time required for the chlorination is about 40 minutes.

The crude reaction product at 50° consists of a reddish yellow upper layer of diethylthiocarbamyl chloride saturated with sulfur (Note 6) and a viscous lower layer of amorphous sulfur saturated with diethylthiocarbamyl chloride. The mechanical stirrer is replaced by a 6-in. glass-helix-packed column arranged for distillation. A magnetic stirrer is used throughout the distillation. The diethylthiocarbamyl chloride is distilled under reduced pressure, b.p. 80–85°/1 mm. (Notes 7 and 8), m.p. 48–51°. The yield is 71–72 g. (93–95%) (Notes 9 and 10).

2. Notes

1. A tube of smaller diameter may be used, but a tube 10 mm. in diameter is recommended to minimize plugging.

2. The hood serves to carry away unabsorbed chlorine and diethylthiocarbamyl chloride vapors. The fumes are irritating to the eyes, nose, and throat and may have other injurious physiological effects.

3. The quality of the product depends to a large extent upon the purity of the tetraethylthiuram disulfide used. Since the yield is decreased in proportion to the quantity of water present, reagents used should be dry. Dry Sharples Tetraethylthiuram Disulfide No. 163 was found to be satisfactory without further purification.

4. An alternative method is to add chlorine to a solution or suspension of tetraethylthiuram disulfide in an inert liquid medium such as carbon tetrachloride. If the quantity and nature of the solvent are such as to dissolve the diethylthiocarbamyl chloride, most of the liberated sulfur can be separated mechanically and the chloride isolated by distillation after evaporation of the solvent.

5. As the chlorination progresses, the melting point of the reaction mass becomes lower so that after about one-third of the theoretical quantity of chlorine has been added the temperature may be dropped to 50°, which is approximately the melting point of the final product. The low temperature is desirable because there is less danger of overheating at the point of entry of the chlorine.

6. If the crude product is held at 50–55° for 6–8 hours, approximately 70% of the theoretical amount of free sulfur precipitates and may be separated by decantation and filtration. The remaining 30% of the theoretical quantity of sulfur remains in solution in the diethylthiocarbamyl chloride.

7. Good fractionation is not necessary, and a better product can usually be obtained by a rapid distillation than by a slow distillation at a high reflux ratio. A column with a 6- or 8-in. packed section gives a sufficiently pure product for most purposes.

The distillation may be carried out at higher pressures with only slightly more decomposition. At a pressure of 13–14 mm. diethylthiocarbamyl chloride distils at 117–120°. If the pot temperature is above 140° decomposition becomes appreciable, and at 160–190° a vigorous decomposition occurs, especially when a relatively large amount of sulfur is present.

8. The crude diethylthiocarbamyl chloride need not be distilled if sulfur does not interfere in the reaction for which the chloride is to be used and if sulfur can be readily separated from the product. At approximately 105° all the sulfur liberated by the chlorination of tetraethylthiuram disulfide will dissolve in the diethylthiocarbamyl chloride, forming a homogeneous product which may be used on the basis of 100% conversion of the disulfide to the chloride.

9. The submitters used a scale 10 times larger than that given here and obtained yields of 89–94%.

10. The submitters have prepared the following thiocarbamyl chlorides by the chlorination of the corresponding disulfides: dimethylthiocarbamyl chloride, b.p. 90–95°/0.5 mm., m.p. 42.5–43.5°, carbon tetrachloride reaction medium; diisopropylthiocarbamyl chloride, m.p. 69–71°, benzene reaction medium; diisobutylthiocarbamyl chloride, m.p. 46–48°, no solvent.

3. Methods of Preparation

Billeter prepared diethylthiocarbamyl chloride[2] and other carbamyl chlorides[3,4] by the reaction of the appropriate amine as amine hydrochloride with thiophosgene. The present preparation represents an adaptation of the Ritter process.[5]

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[1] Pennsylvania Salt Manufacturing Company, Wyndmoor, Pennsylvania.

[2] Billeter, *Ber.*, **26**, 1681 (1893).

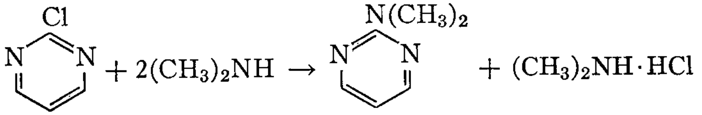
[3] Billeter, *Ber.*, **20**, 1629 (1887).

[4] Mazzara, *Gazz. chim. ital.*, **23**, I, 37 (1893) [*Chem. Zentr.*, **64**, I, 647 (1893)].

[5] Ritter, U. S. pat. 2,466,276 [*C. A.*, **43**, 5038 (1949)].

2-(DIMETHYLAMINO)PYRIMIDINE

(Pyrimidine,2-dimethylamino-)



Submitted by C. G. Overberger, Irving C. Kogon, and Ronald Minin.[1]
Checked by Charles C. Price and T. L. V. Ulbricht.

1. Procedure

In a 250-ml. three-necked flask equipped with a reflux condenser and a gas-inlet tube are placed 45.6 g. (0.4 mole) of 2-chloropyrimidine[2] and 150 ml. of absolute ethanol. The mixture is refluxed for 6 hours while anhydrous dimethylamine is bubbled into the solution (Note 1). The solution is cooled, and 100 ml. of ethanol is removed by distillation using a water aspirator. The residue is chilled in an ice bath for 1 hour, and 75 ml. of ether is added to cause precipitation of dimethylamine hydrochloride. After the removal of dimethylamine hydrochloride and solvent, the residue is distilled at reduced pressure from a Claisen flask (Note 2). The fraction boiling at 85–86°/28 mm. is collected; yield 40–42.5 g. (81–86%), n_D^{25} 1.5420 (Note 3).

2. Notes

1. Anhydrous dimethylamine may be conveniently prepared by allowing 25% aqueous dimethylamine to drop onto solid potassium hydroxide, the gas evolved being dried by passage over solid potassium hydroxide.

2. The compound is hygroscopic, and care should be taken to prevent exposure to air.

3. N-Methylaminopyrimidine is similarly prepared; b.p. 96–98°/28 mm., m.p. 57.5–58.5° (65% yield).

3. Methods of Preparation

Similar procedures for this preparation have been reported by Brown and Short[3] and by Copenhaver and Kleinschmidt.[4]

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[1] Department of Chemistry, Polytechnic Institute of Brooklyn, Brooklyn 2, New York.

[2] *Org. Syntheses*, **35**, 34 (1955).

[3] Brown and Short, *J. Chem. Soc.*, **1953**, 331.

[4] Copenhaver and Kleinschmidt, Brit. pat. 663,303 [*C. A.*, **46**, 10212 (1952)].

ETHYL DIETHOXYACETATE

(Glyoxylic acid, ethyl ester, diethyl acetal)

$$\mathrm{Cl_2CHCO_2H + 3CH_3CH_2ONa \rightarrow (CH_3CH_2O)_2CHCO_2Na + 2NaCl + 3CH_3CH_2OH}$$

$$\mathrm{(CH_3CH_2O)_2CHCO_2Na + CH_3CH_2OH + HCl \rightarrow (CH_3CH_2O)_2CHCO_2CH_2CH_3 + NaCl + H_2O}$$

Submitted by Robert Bruce Moffett.[1]
Checked by Charles C. Price and Charles E. Scott.

1. Procedure

A 2-l. three-necked flask (Note 1), fitted with a sealed stirrer (Note 2) and an efficient reflux condenser (protected by a calcium chloride tube), is surrounded by a water bath. Sodium ethoxide is prepared in this flask by adding 31 g. (1.35 gram atoms) of sodium in portions to 450 ml. of absolute ethanol (Note 3). When practically all the sodium has dissolved, 50 g. (0.39 mole) of dichloroacetic acid is added with stirring at such a rate that the solvent refluxes smoothly. About 20 minutes is required. Sodium chloride soon begins to separate, and the solution becomes a yellow-orange color. After the initial reaction subsides, the mixture is heated under reflux with stirring for 3.5 hours.

The water is removed from the water bath and replaced by an ice-salt mixture. A thermometer is placed in the flask with the bulb below the surface of the liquid, and the mixture is cooled below 0°. Then a solution of about 27 g. (0.75 mole) of hydrogen chloride in 200 ml. of absolute ethanol (Note 4) is slowly added (Note 5) during about 40 minutes with stirring and cooling at such a rate that the temperature does not rise above 10°. The mixture is allowed to come to room temperature, and the stirring is continued for 3 hours. It is then allowed to stand overnight. The reaction mixture is again cooled to 0°, and the excess acid is neutralized to approximately *p*H 7 by slowly adding sodium ethoxide solution (Note 6). The mixture is tested from time to time during the addition of the alkali by placing a drop on moistened *p*H test paper. About 75 ml. of sodium ethoxide solution is required. The mixture is then filtered through a large Büchner funnel (Note 7), and the precipitate is extracted thoroughly with ether which is added to the alcoholic filtrate. The solid is discarded.

Most of the solvent is removed by distillation through a Vigreux column under reduced pressure (about 40 mm.) and a pot temperature less than 40°. The product is then transferred to a smaller flask (Note 8). The remainder of the solvent is removed through the Vigreux column at a pressure of about 15 mm. and a boiling point up to about 40°. A Dry Ice-cooled receiver (Note 9) is then attached, and the pressure is lowered by means of a high-vacuum pump. The crude product is distilled until no more material comes over while the flask is heated on a steam bath. This crude product, b.p. 87–88°/17 mm., 69–70°/10 mm., n_D^{25} 1.4073–1.4076, may be redistilled, a pinch of calcium carbonate being added, through an efficient column (Note 10) at a pressure of about 12 mm. The fore-run (boiling point up to about 60°/12 mm.) is discarded. The fraction, b.p. 60–81°/12 mm., is saved for redistillation with a subsequent run. The main fraction is obtained at a boiling range of 81–83°/12 mm. The yield of ethyl diethoxyacetate is 31–34 g. (45–50%) of colorless liquid, n_D^{25} 1.4075.

2. Notes

1. The submitters report equally satisfactory results when the reaction is carried out in a 12-l. flask on ten times the scale described here.
2. A Hershberg stirrer is excellent for the purpose and may be connected by a mercury seal or a rubber seal lubricated with glycerol.[2, 3]
3. The absolute ethanol is dried with sodium and diethyl phthalate.[4]
4. The alcoholic hydrogen chloride can be prepared by passing hydrogen chloride from a cylinder (use safety trap) into 200 ml. of absolute ethanol cooled by an ice bath. From time to time a sample may be withdrawn and titrated with standard alkali to determine the concentration. The exact amount is not critical, but a considerable excess of hydrogen chloride must be used. If several runs are to be made it is convenient to prepare a large quantity of alcoholic hydrogen chloride at one time.
5. Precautions should be taken to prevent absorption of atmospheric moisture by the hydrogen chloride solution. The dropping funnel should be closed or protected by a calcium chloride tube.
6. Enough sodium ethoxide solution for four runs can be made in a 500-ml. flask by adding 18.4 g. of sodium portionwise to 300 ml. of absolute ethanol.
7. If difficulty in the filtration is encountered a filter aid may be used.
8. At this point it is convenient to combine several runs for distillation.
9. The Dry Ice-cooled receiver is conveniently constructed

from a two-necked round-bottomed flask immersed up to the necks in a Dry Ice-ethanol mixture.

10. The submitters used a column packed with 12 in. of ⅛-in. glass helices and fitted with a variable reflux head. The checkers used a 12-in. Vigreux column.

3. Methods of Preparation

Ethyl diethoxyacetate has been prepared from dichloroacetic acid by the action of sodium ethoxide followed by esterification of the intermediate diethoxyacetic acid. This esterification has been carried out with ethyl iodide on the sodium salt or on the silver salt.[5,6,7] It has been more conveniently done with ethanol and acid.[8,9,10] Poorer yields are reported when the dichloroacetic acid is first esterified and then treated with sodium ethoxide.[11]

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[1] The Upjohn Company, Kalamazoo, Michigan.

[2] *Org. Syntheses* Coll. Vol. **3**, 368 (1955).

[3] *Org. Syntheses*, **30**, 54 (1950).

[4] *Org. Syntheses* Coll. Vol. **2**, 155 (1943).

[5] Schreiber, *Z. Chem.*, **1870**, 167; *Jahresber. Fortschr. Chem.*, **1870**, 642.

[6] Johnson and Cretcher, Jr., *J. Biol. Chem.*, **26**, 106 (1916).

[7] Rugeley and Johnson, *J. Am. Chem. Soc.*, **47**, 2997 (1925).

[8] Wohl and Lange, *Ber.*, **41**, 3612 (1908).

[9] Blaise and Picard, *Bull. soc. chim.*, [4] **11**, 539 (1912).

[10] Johnson and Cretcher, Jr., *J. Am. Chem. Soc.*, **37**, 2147 (1915).

[11] Cope, *J. Am. Chem. Soc.*, **58**, 570 (1936).

ETHYL ISOCYANIDE

$$C_2H_5I + AgCN \rightarrow C_2H_5NC\cdot AgI$$

$$C_2H_5NC\cdot AgI + 2KCN \rightarrow C_2H_5NC + KAg(CN)_2 + KI$$

Submitted by H. L. Jackson and B. C. McKusick.[1]
Checked by N. J. Leonard and L. E. Coleman, Jr.

1. Procedure

Caution! This preparation should be carried out in a well-ventilated hood because ethyl isocyanide has a vile odor. Since ethyl

isocyanide has been known to explode,[2] all operations in which it is heated, including its distillation, should be carried out behind a shield of safety glass.

Silver cyanide (454 g., 3.40 moles) is added with stirring to 530 g. (3.40 moles) of ethyl iodide in a 3-l. three-necked round-bottomed flask, equipped with a reflux condenser and a sealed Hershberg stirrer. The third neck of the flask is closed with a stopper. The lower third of the flask is immersed in a steam bath, and the mixture is stirred vigorously until it turns to a viscous, homogeneous, brown liquid (1.7–2.3 hours). Stirring is interrupted, the steam bath is removed, and the stirrer is raised to a position just above the liquid (Note 1). Water (300 ml.) is added through the condenser to avoid loss of product during the addition. Potassium cyanide (610 g., 9.37 moles) and 260 ml. of water are then added through the third neck of the flask, and the mixture is stirred for about 10 minutes, during which the heavy brown liquid below the aqueous solution disappears and a brown layer of ethyl isocyanide appears above the aqueous solution. Stirring is discontinued, the reflux condenser is replaced by one arranged for distillation, and a thermometer extending into the aqueous layer is placed in the third neck. A receiver immersed in an ice bath is attached to the condenser, and the reaction mixture is heated by means of an electric heating mantle, causing a mixture of oil and water to distil. When the distillate contains almost no oil (Note 2), the distillation is discontinued (Note 3). The receiver contains about 200 ml. of crude ethyl isocyanide and 50 ml. of water. Sodium chloride (7 g.) is dissolved in the aqueous layer, and the ice-cold mixture is poured into a separatory funnel. The aqueous layer is separated and discarded. The ethyl isocyanide is washed with two 50-ml. portions of ice-cold saturated aqueous sodium chloride solution and is dried overnight with 10 g. of anhydrous magnesium sulfate. The decanted material is distilled through a 5- to 10-plate column (Note 4), giving 88–102 g. (47–55% yield) of ethyl isocyanide, b.p. 77–79°/760 mm., n_D^{20} 1.3632. The fore-run, b.p. 63–77°/760 mm., amounts to 15–46 g. and contains 10–15% of ethyl iodide and possibly a few drops of water. Additional pure ethyl isocyanide can be obtained by drying and redistilling this fore-run.

2. Notes

1. Sometimes the liquid crystallizes to a dense solid which immobilizes the stirrer if it has not been raised. The crystallization has no effect on subsequent steps except to necessitate a longer period of stirring after the potassium cyanide is added.
2. The temperature of the residual mixture is 115–120° at this point.
3. The aqueous cyanide solution, which is very toxic, can be disposed of by flushing it down the drain with a large volume of water.
4. The submitters used an 18-in. spinning-band column (inside diameter 10 mm.). The checkers employed a 12-in. helix-packed column.

3. Methods of Preparation

Ethyl isocyanide has been obtained by treating ethylamine and chloroform with potassium hydroxide,[3] by pyrolyzing the complex between ethyl isothiocyanate and triethylphosphine,[4] by heating cyanocobaltic (III) acid with ethanol,[5] by passing ethylene and hydrogen cyanide through an electric discharge,[6] or by heating ethyl iodide with silver cyanide [7,8,9] or other metal cyanides.[8,10] The present procedure differs from earlier ones using silver cyanide mainly in that a stirrer is employed. By this modification more than half of the silver cyanide can be converted to ethyl isocyanide, contrary to the belief of the earlier workers, who thought that this was precluded by formation of a complex, $C_2H_5NC \cdot AgCN$.

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[1] Chemical Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware.

[2] Lemoult, *Compt. rend.*, **143**, 902 (1906).

[3] Hofmann, *Ann.*, **146**, 109 (1868).

[4] Hofmann, *Ber.*, **3**, 766 (1870).

[5] Hölzl, Meier-Mohar, and Viditz, *Monatsh.*, **53–54**, 237 (1929).

[6] Francesconi and Ciurlo, *Gazz. chim. ital.*, **53**, 327 (1923).

[7] Gautier, *Ann. chim. et phys.*, [4] **17**, 233 (1869).

[8] Guillemard, *Ann. chim. et phys.*, [8] **14**, 363 (1908).

[9] Lowry and Henderson, *Proc. Roy. Soc.* (*London*), **A136**, 487 (1932).

[10] Guillemard, *Bull. soc. chim. France*, [4] **1**, 530 (1907).

ETHYL N-PHENYLFORMIMIDATE

(Formimidic acid, N-phenyl-, ethyl ester)

$$C_6H_5NH_2 + (C_2H_5O)_3CH \xrightarrow{H^+} C_6H_5N{=}CHOC_2H_5 + 2C_2H_5OH$$

Submitted by Royston M. Roberts and Paul J. Vogt.[1]
Checked by T. L. Cairns and J. J. Drysdale.

1. Procedure

A 500-ml. flask is equipped with a capillary through a side opening, and 94 g. (1.01 moles) of aniline and 1 ml. of concentrated hydrochloric acid are added. A 12-in. glass-helix-packed column is attached (Note 1), and the water introduced with the acid is removed by boiling; about 1 ml. of aniline is collected after the water has distilled. The flask and its contents are then cooled to room temperature, and 222 g. (1.50 moles) of ethyl orthoformate is added. The column is reattached, and ethanol (Note 2) is distilled as it is produced; the theoretical amount (92 g., 116 ml.) is obtained in about 2.25 hours.

The reaction mixture is allowed to cool slightly, and the pressure is lowered to 40 mm. (Note 3). The excess ethyl orthoformate is distilled at 65°/40 mm. After a small intermediate fraction of about 4 g., b.p. 65–117°/40 mm., the product distils at 117–118°/40 mm. (b.p. 87–88°/10 mm.; n_D^{25} 1.5248); the yield is 118–127 g. (78–84%). The residue is about 14 g. and is mainly N,N′-diphenylformamidine (Note 4).

2. Notes

1. A Vigreux column may also be used since it is not difficult to separate the ethanol from ethyl orthoformate, the next most volatile component present. A total reflux, partial take-off head was used. Heat was supplied by an electric mantle; the column was heated with a glass-covered heating tape during the distillation of excess ethyl orthoformate and product.

2. A small amount (5–10 ml.) of lower-boiling material usually comes over before the ethanol; this is probably ethyl formate, produced by hydrolysis of the ethyl orthoformate.

3. A pressure regulator may conveniently be used in conjunction with a water aspirator.

4. If several runs are to be made, the residue may be saved and used as starting material, since the reaction proceeds via the initial formation of N,N′-diphenylformamidine and its subsequent reaction with ethyl orthoformate.[2,3]

3. Methods of Preparation

Ethyl N-phenylformimidate has been prepared from silver formanilide and ethyl iodide,[4] and from aniline and ethyl orthoformate.[3] This method incorporates the discovery[2] of the necessity of acid catalysis for satisfactory yields by the latter process.

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[1] Department of Chemistry, University of Texas, Austin, Texas.

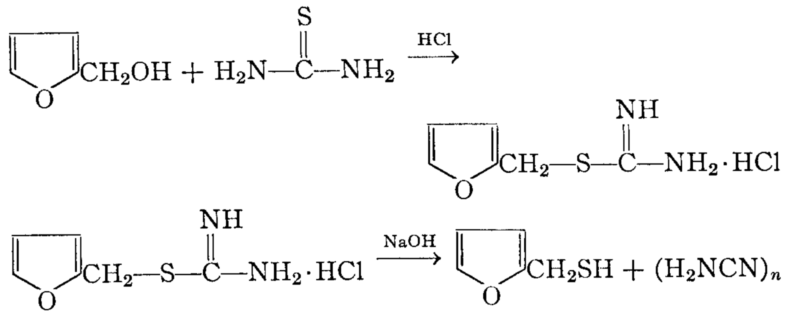
[2] Roberts, *J. Am. Chem. Soc.*, **71**, 3848 (1949).

[3] Claisen, *Ann.*, **287**, 363 (1895).

[4] Comstock and Clapp, *Am. Chem. J.*, **13**, 527 (1891).

2-FURFURYL MERCAPTAN

(2-Furanmethanethiol)



Submitted by Helmer Kofod.[1]
Checked by Richard T. Arnold and Erich Marcus.

1. Procedure

Caution! The following operations should be carried out in an effective hood (Note 1).

In a 3-l. round-bottomed flask are placed 380 g. (5 moles) of thiourea (Note 2), 500 ml. of water, and 400 ml. of concentrated hydrochloric acid (12.5 *N*) (Note 3). The solid is dissolved by gentle heating, and the solution is cooled to 30°. Furfuryl alcohol (490 g., 434 ml., 5 moles) (Note 4) is added to the reaction mixture. The reaction, which usually commences spontaneously within a few minutes (Note 5), is strongly exothermic and should be controlled by suitable cooling with tap water so as to hold the temperature near 60° (Note 6). When the reaction subsides, cooling is discontinued and the clear, dark green solution is allowed to stand at room temperature for 12 hours.

A solution of 225 g. of sodium hydroxide (Note 3) in 250 ml. of water is poured into the reaction mixture. A heavy brown oil separates, consisting of S-2-furfurylisothiourea, which has already partially decomposed to 2-furfuryl mercaptan. The flask is quickly fitted with a steam-inlet tube and condenser. Steam distillation is continued as long as the distillate contains oily drops. The mercaptan is separated from the aqueous phase by means of a separatory funnel (Notes 7 and 8). The product is dried with calcium chloride; yield, 313–340 g. (55–60%). The 2-furfuryl mercaptan so obtained is of a high degree of purity (Note 9) but can be distilled without decomposition in a nitrogen atmosphere; b.p. 160°/759 mm., 84°/65 mm., n_D^{20} 1.533.

2. Notes

1. The odor of the mercaptan is extremely disagreeable, and the substance in high concentration causes headache. An effective hood is absolutely essential.

2. The checkers employed practical-grade thiourea obtained from Matheson, Coleman and Bell, East Rutherford, New Jersey.

3. It is desirable to determine the exact concentration of the hydrochloric acid and the composition of the sodium hydroxide by titration.

4. The checkers employed practical-grade furfuryl alcohol obtained from the Eastman Kodak Company.

5. If the reaction does not start, the flask is heated gently until a spontaneous temperature rise sets in.

6. Temperatures above 60° and particularly supplementary refluxing are to be avoided since under these conditions the sensitive furan ring is attacked.

7. The mercaptan is almost insoluble in water, and the aqueous phase contains too little product to justify extraction.

8. It is convenient to use a 2-l. separatory funnel as a receiver during the steam distillation.

9. The checkers found the undistilled product to be essentially pure; n_D^{25} 1.5285. The distilled material was obtained with only mechanical losses; b.p. 84°/65 mm., n_D^{25} 1.5280.

3. Methods of Preparation

Furfuryl mercaptan cannot be prepared according to the classical method using furfuryl chloride and potassium sulfide.[2] It has been prepared by reduction of 2-furfuryl disulfide, obtained from furfural and ammonium hydrosulfide.[3] The mercaptan has also been obtained in 33% yield [2] by the reaction of furfuryl chloride with thiourea and subsequent decomposition of the intermediate S-2-furfurylisothiourea according to the general method described in *Organic Syntheses*.[4] In the present method, which has been published previously, the use of the very unstable and difficultly available furfuryl halides is avoided.[5]

The formation of mercaptans directly from alcohols may be applied to the preparation of a large number of mercaptans, but usually much longer reaction periods or higher temperatures and higher concentrations of hydrogen halides are required.[6] Under such conditions the furan ring is destroyed.

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[1] Danmarks farmaceutiske Højskole, Copenhagen, Denmark.

[2] Kirner and Richter, *J. Am. Chem. Soc.*, **51**, 3131 (1929).

[3] Staudinger and Reichstein, Can. pat. 283,765 [*C. A.*, **22**, 4537 (1928)].

[4] *Org. Syntheses* Coll. Vol. **3**, 363 (1955).

[5] Kofod, *Acta Chem. Scand.*, **7**, 1302 (1953).

[6] Frank and Smith, *J. Am. Chem. Soc.*, **68**, 2103 (1946).

GUANYLTHIOUREA

(Urea, 2-thio-3-guanyl-)

$$NH_2C(NH)NHCN + H_2S \rightarrow NH_2C(NH)NHCSNH_2$$

Submitted by Frederick Kurzer.[1]
Checked by John C. Sheehan, George Buchi, and David Knutson.

1. Procedure

A 500-ml. three-necked round-bottomed flask, supported in a water bath equipped with a thermostat, is fitted with a vertical air-condenser and, on the side necks, with a thermometer and a gas delivery tube, both of which nearly reach the bottom of the vessel. The flask contains a solution of 42 g. (0.5 mole) of N-cyanoguanidine (dicyandiamide) (Note 1) in 200 ml. of water (Note 2). This is kept at 75° during 12 hours, and at 65–70° during an additional 25–30 hours (Note 3) while a fairly slow stream (Note 4) of hydrogen sulfide is passed through (Note 5). The resulting deep yellow liquid is allowed to cool to 45° while passage of hydrogen sulfide is continued; it is made strongly alkaline with 15 ml. of 40% aqueous sodium hydroxide and is freed from suspended impurities (consisting usually of finely divided black particles) by rapid filtration under reduced pressure (Note 6). The clear, yellow filtrate is allowed to cool slowly to room temperature, when lustrous prismatic leaflets separate gradually. Crystallization is completed by storing the flask and contents at 0° for 24 hours. The crystalline mass is broken up with a spatula, collected by filtration, and washed with three 20-ml. portions of ice water, the second and third portions of washing liquid being collected separately and discarded (Note 7). The yield of crude guanylthiourea, forming large, nearly colorless prisms, m.p. 160–164° (dec., with previous sintering at 154–158° or somewhat lower) (Note 8), varies between 29.5 and 32.5 g. (50–55%).

The material is purified as follows: The large crystals are powdered (Note 9) and boiled with successive portions of methanol until solution is complete, the saturated extracts being decanted and collected; approximately 8–9 ml. of methanol per gram of crude solid is required. The combined hot solution is filtered, if necessary, with suction, is allowed to cool slowly to room temperature, and is then stored at 0° overnight. Almost pure guanylthiourea, forming colorless prisms, m.p. 170–172° (dec., with previous sintering in the range 166–170°), is collected by filtration and washed with a little methanol. The recovery, per crystallization, varies from 65% to 70%. Most of the material contained in the mother liquors may be obtained by evaporation to small volume (Note 10) and forms one or two crops of satisfactory quality (melting point ranging between 166° and 170°).

2. Notes

1. A good reagent grade of N-cyanoguanidine is satisfactory in this synthesis.

2. The smallest possible volume of water is employed to ensure direct crystallization of the product when the solution is finally allowed to cool. Smaller volumes than the stated amount of water, however, tend to block the delivery tube with separated crystalline material, particularly in the beginning stages of the reaction, when much of the less-soluble reactant is still present.

3. The total time of heating may be made up of several shorter periods. On being cooled overnight the reaction mixture deposits a thick crust of crystalline solid on the walls of the flask. After 8 hours, large, spikelike prisms of unchanged N-cyanoguanidine predominate, but later the separated mass consists of massive rhombic prisms of guanylthiourea, with small needles of 2,4-dithiobiuret filling the spaces between the prisms. Solution is once again rapidly effected when the temperature is raised to 70°, with passage of hydrogen sulfide.

4. A rate of 3–4 bubbles of hydrogen sulfide per second is satisfactory. Towards the end of the time of reaction, a slower stream suffices.

5. Since hydrogen sulfide is only slowly absorbed, most of the gas escapes through the air condenser. The reaction must therefore be performed in an efficient hood.

6. A preheated Büchner flask and filter of 5- to 7-cm. diameter carrying a double layer of filter paper are employed.

7. 2,4-Dithiobiuret may be isolated from the alkaline filtrate as follows: The stirred alkaline filtrate is acidified to Congo red with 25–30 ml. of concentrated hydrochloric acid. A pale yellow powdery solid is rapidly precipitated, with evolution of hydrogen sulfide; after storage at 0°, the solid (dry weight 7.5–9.0 g.) is collected by filtration, washed three times with 30-ml. portions of ice water, and pressed semidry. This material is added to boiling water (100 ml.) and stirred at 95–100° for 2 minutes, and the undissolved yellow powdery impurities (1.0–1.5 g., consisting largely of sulfur) are quickly removed by filtration with suction through a preheated funnel. The clear, pale yellow filtrate is rapidly filled with crystals, which are collected after storage at 0° for 12 hours. The yield of crude 2,4-dithiobiuret, forming small yellow needles, m.p. 178–180° (dec., previously sintering at 172–175°) is 5.5–7.0 g. (8–10%) (Note 11). Two crystallizations from boiling water (12 ml. per gram, recovery per crystallization: 80–90%) (Note 12), one with addition of carbon, affords nearly white lustrous needles of 2,4-dithiobiuret, m.p. 180–182° (dec., previously sintering slightly at 178–180°) (Note 13).

8. Colorless guanylthiourea melts to a pale yellow liquid, which resolidifies to a yellow crystalline mass on cooling; partial rearrangement to guanidine thiocyanate occurs during the fusion.

9. When ground in a mortar, the crude guanylthiourea evolves small quantities of occluded hydrogen sulfide.

10. The methanolic filtrates are rapidly distilled to approximately half volume at low temperature in a good vacuum. The solution is likely to froth considerably, and the use of a relatively large distilling flask is recommended. Small quantities of solid separating on the walls of the flask are redissolved by heating the residual liquid once again on a steam bath.

11. The yield of dithiobiuret increases on lengthening the time of reaction. After 100 hours' passage of hydrogen sulfide the

yields of guanylthiourea and dithiobiuret were 25–35% and 15–18%, respectively.

12. Crystallization is carried out by adding the solid to the appropriate volume of boiling water, stirring at 95–100° for about 1 minute, and removing small quantities of suspended yellow impurities by filtration under reduced pressure using carefully preheated apparatus. When cooled slowly, the clear filtrate deposits the product in the form of large, lustrous needles.

13. On analysis, this material gives carbon, hydrogen, nitrogen, and sulfur percentages in excellent agreement with the calculated values. Two additional crystallizations from ethanol-water (10 ml. each, per gram) raise the melting point to 183–185° (dec.). These decomposition temperatures are somewhat influenced by the rate of heating; the quoted values are observed when the specimen is inserted at 160° and the bath temperature is raised at the approximate rate of 8° per minute.

3. Methods of Preparation

Guanylthiourea has been prepared by the prolonged interaction of saturated aqueous hydrogen sulfide with N-cyanoguanidine [2,3] or an amidinourea salt [4] at 60–80°. It is formed in small quantities when thiourea is heated with thiophosgene or phosphorus pentachloride at 100–110°.[5] Guanylthiourea also results from the acid hydrolysis of 4,6-diamino-2-thio-1,3,5-thiadiazine.[6,7] In all these syntheses the product is collected as a sparingly soluble salt, the base being subsequently isolated by comparatively laborious methods, e.g. from the oxalate [2] or the phosphate.[7] The present procedure,[8] based on Bamberger's method,[2] allows the direct isolation of the base. Small quantities of 2,4-dithiobiuret, which are also formed in this reaction as a by-product, are readily separated.

[1] Royal Free Hospital School of Medicine, University of London, England.

[2] Bamberger, *Ber.*, **16**, 1460 (1883).

[3] Slotta and Tschesche, *Ber.*, **62**, 1402 (1929).

[4] Bamberger, *Ber.*, **16**, 1461 (1883).

[5] Rathke, *Ber.*, **11**, 962 (1878).

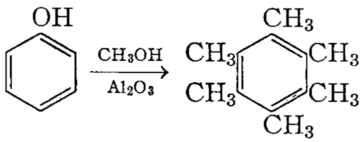
[6] Thurston and Sperry, U. S. pat. 2,364,594 [*C. A.*, **39**, 4630 (1945)].

[7] Birtwell, Curd, Hendry, and Rose, *J. Chem. Soc.*, **1948**, 1653.

[8] Kurzer, *J. Chem. Soc.*, **1955**, 1.

HEXAMETHYLBENZENE

(Benzene, hexamethyl-)



Submitted by N. M. Cullinane, S. J. Chard, and C. W. C. Dawkins.[1]
Checked by T. L. Cairns and D. C. England.

1. Procedure

A solution of 100 g. (1.06 moles) of phenol in 1 l. of methanol is allowed to drop at a rate of 110 ml. per hour (Note 1) over an activated alumina catalyst (Note 2) heated to 530° (Note 3). The exit from the hot tube is attached to a receiver arranged to lead by-product gases to an efficient hood (Note 4). After addition of the methanol solution is finished, the pale yellow product is transferred to a Büchner funnel and washed with methanol. The yield of crude product melting at 135–145° is 112–115 g. (65–67%). Recrystallization from ethanol (50 g. in 650 ml.) gives 85% recovery or from benzene (50 g. in 130 ml.) gives 60% recovery of colorless hexamethylbenzene, m.p. 165–166°.

2. Notes

1. The submitters used a rate of 250 ml. per hour with a 2-in.-diameter tube, 16 in. long, packed with 300 g. of alumina, and a temperature in the catalyst bed about 370–380°. The checkers used 34 g. of alumina packed in a ⅞-in.-diameter tube 13 in. long.

2. The submitters used 4- to 8-mesh alumina from Peter Spence and Sons, Widnes, Lancashire, England. The checkers used 8- to 14-mesh Alorco H-41 obtained from the Aluminum Company of America, 1200 Alcoa Building, Pittsburgh 19, Pennsylvania.

3. Automatically controlling the outside of the catalyst tube to 370–400° gives a hot spot in the catalyst bed of 530° at the rate specified in equipment used by the checkers.

4. Gases formed in the reaction included carbon monoxide, methane, and hydrogen. The exact equation for the reaction is not known.

3. Methods of Preparation

Hexamethylbenzene has been prepared by passing the mixed vapors of acetone and methanol over alumina at 400°.[2] Briner, Plüss, and Paillard [3] have obtained it by passing different phenols mixed with methanol in an atmosphere of dry carbon dioxide over alumina at 410–440°.

The present method is based on that of Cullinane and Chard.[4]

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[1] University College, Cardiff, Wales.

[2] Reckleben and Scheiber, *Ber.*, **46**, 2363 (1913).

[3] Briner, Plüss, and Paillard, *Helv. Chim. Acta*, **7**, 1046 (1924).

[4] Cullinane and Chard, *J. Chem. Soc.*, **1945**, 821.

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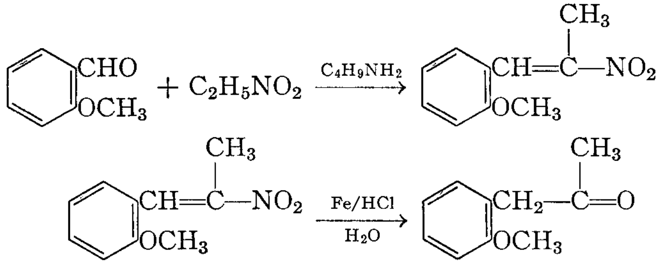
o-METHOXYPHENYLACETONE

[2-Propanone, 1-(*o*-methoxyphenyl)-]



Submitted by R. V. Heinzelman.[1]
Checked by M. Tishler and H. L. Slates.

1. Procedure

A. *1-(o-Methoxyphenyl)-2-nitro-1-propene.* A 1-l. round-bottomed flask is fitted with an electric heating mantle, a modified

Dean and Stark water separator (Note 1), and a reflux condenser. To the flask are added in this order 200 ml. of reagent-grade toluene, 136 g. (1.0 mole) of *o*-methoxybenzaldehyde (Note 2), 90 g. (1.1 moles) of commercial nitroethane (Note 3), and 20 ml. of *n*-butylamine (Note 4). The solution is heated to produce a rapid reflux until the separation of water ceases (Note 5). The toluene solution is used directly in the next step (Note 6).

B. *o-Methoxyphenylacetone.* A 3-l. three-necked round-bottomed flask is equipped with an electric heating mantle, two reflux condensers, a dropping funnel, and a high-speed whip stirrer (Note 7). The toluene solution from Part A is placed in the flask, and 500 ml. of water, 200 g. of powdered iron (Note 8), and 4 g. of ferric chloride are added. With vigorous agitation the suspension is heated to about 75°, and 360 ml. of concentrated hydrochloric acid is added over a 2-hour period (Note 9); heating and stirring are continued for an additional 30 minutes.

The suspension is transferred to a 5-l. three-necked round-bottomed flask and subjected to steam distillation until 7–10 l. are collected (Note 10). The toluene layer is removed, and the aqueous layer is extracted with 1 l. of fresh toluene. The combined toluene layers are agitated for 30 minutes with a solution of 26 g. of sodium bisulfite in 500 ml. of water (Note 11). The toluene layer is washed with water, and the solvent is removed at water-pump pressure on the steam bath. The resulting orange liquid weighs 107–120 g. (65–74%); n_D^{20} 1.5250–1.5270, and is sufficiently pure for most uses. It is purified by distillation through a 12-in. Vigreux column, and the fraction boiling at 128–130°/14 mm. is collected. The yield is 102–117 g. (63–73%, based on the methoxybenzaldehyde used), n_D^{20} 1.5250–1.5260 (Notes 12, 13).

2. Notes

1. The model manufactured by the Corning Glass Works, Corning, New York, and listed as No. 3622 was used. See also *Org. Syntheses*, Coll. Vol. **3**, 382 (1955).

2. *o*-Methoxybenzaldehyde is available from Eastman Kodak Company, Rochester, New York, and from the Matheson Com-

pany, East Rutherford, New Jersey. It may also be prepared according to Baeyer and Villiger.[2]

3. The nitroethane was obtained from Commercial Solvents Corporation, Terre Haute, Indiana, as a 90% pure product. The amount used is a 10% excess based on its nitroethane content. The chief contaminant is 2-nitropropane, which does not interfere in the reaction.

4. It is desirable to swirl the flask after each addition to prevent the formation of layers.

5. Half of the water is collected in about an hour, and the theoretical amount (18 ml.) in about 5 hours. Water removal usually ceases at about 105% of theory. Insufficient reflux rate causes incomplete water removal or an unduly prolonged reaction time.

6. The pure nitroölefin can be obtained by removing the toluene on the steam bath at water-pump pressure and recrystallizing the resulting oil from ethanol or petroleum ether. With petroleum ether, particularly, the volume should be great enough that the product remains in solution until the solution temperature is sufficiently low to prevent oiling out. Addition of seed crystals will encourage crystallization. Alternatively, the yellow oil may be distilled at reduced pressure. The nitroölefin boils at 135–138°/1 mm. and crystallizes in the receiver when seeded. The yield is 150–175 g. (80–90%). The yellow crystals melt at 51–52° when pure. Although no difficulty has been experienced with this compound, the usual safety precautions should be observed when distilling an unsaturated nitro compound. The material is somewhat lachrymatory and irritates the skin.

7. Rapid agitation is necessary to keep the iron in suspension and to mix the two liquid layers.

8. A 40-mesh grade was used, but material up to 100 mesh has been used successfully. However, with the finer material the reaction is somewhat more vigorous.

9. The reaction mixture should reflux vigorously. When the addition time is increased to 6 hours, the yield is not appreciably changed. The iron-acid ratio appears to be important; however,

doubling the amounts of both ingredients produces no change in yield.

10. The 5-l. flask is either heated with an electric mantle or placed on a steam bath to prevent condensation of steam and increase in volume of the suspension. The steam distillation must be continued beyond the point at which the distillate becomes clear.

11. The bisulfite treatment removes any aldehydic material present at this point. Since this ketone is quite inert to sodium bisulfite, the yield is not lowered by this procedure.

12. The pure ketone has a n_{D}^{20} 1.5240 and a boiling point of 128–130°/14 mm., 150°/30 mm. Insufficient removal of *o*-methoxybenzaldehyde will cause the refractive index to be high to the extent of about 0.0003 for each per cent present. The use of distilled nitroölefin eliminates the aldehyde, but this advantage is offset by the distillation hazard and slightly lower over-all yields.

13. This procedure is quite general for other aromatic aldehydes. An excess of bisulfite must be avoided in the washing step, since many phenyl-substituted acetones react appreciably with it.

3. Methods of Preparation

The present procedure is that described by the submitter.[3] It is an improved modification of that described by Hoover and Hass[4] for the corresponding *para* isomer. *o*-Methoxyphenylacetone has also been prepared from the glycidic ester.[5]

[1] The Upjohn Company, Kalamazoo, Michigan.

[2] Baeyer and Villiger, *Ber.*, **35**, 3023 (1902); Spath, *Monatsh.*, **34**, 1995 (1917).

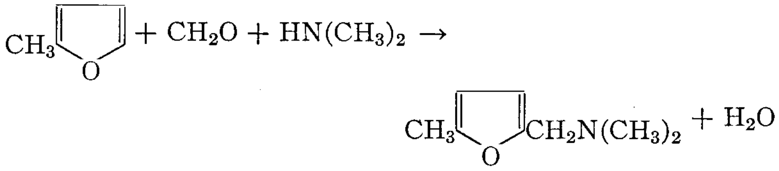
[3] Heinzelman, *J. Am. Chem. Soc.*, **75**, 921 (1953); U. S. pats. 2,557,051 (1951) and 2,601,282 (1952).

[4] Hoover and Hass, *J. Org. Chem.*, **12**, 501 (1947).

[5] Wolf, Ger. pat. 752,328 (1950) [*C. A.*, **45**, 1626 (1951).]

5-METHYLFURFURYLDIMETHYLAMINE

(Furfurylamine, N,N,5-trimethyl-)



Submitted by Ernest L. Eliel and Milton T. Fisk.[1]
Checked by James Cason, Mary S. Nakata, and William G. Dauben.

1. Procedure

To 200 ml. of glacial acetic acid in a 1-l. round-bottomed flask is added slowly, with cooling in an ice bath, 151 ml. (54 g. of dimethylamine, 1.2 mole) of 40% aqueous dimethylamine solution, followed by 90 ml. (36 g. of formaldehyde, 1.2 mole) of 37% aqueous formaldehyde (formalin) solution. The flask is removed from the ice bath and equipped with a reflux condenser, through which 82 g. (90 ml., 1 mole) of 2-methylfuran (Note 1) is added all at once. Upon gentle swirling of the flask, an exothermic reaction may set in spontaneously; if it does not, the flask is heated on a steam bath until reaction commences. In any event, the spontaneous reaction is allowed to proceed without further external heating. When it ceases, the reaction mixture is heated on a steam bath for another 20 minutes, cooled, and without delay poured into a cold solution of 250 g. of sodium hydroxide (Note 2) in 800 ml. of water.

The reaction mixture is steam-distilled until the distillate is only faintly alkaline (Note 3). To the distillate is added sodium hydroxide (Note 2) to the extent of 10 g. for each 100 ml. of distillate. The strongly alkaline solution is cooled and extracted with two 300-ml. portions of ether. The combined ether layers are dried over 25 g. of solid potassium hydroxide (Note 4), decanted, and concentrated. The residue is distilled under reduced pressure; the yield of 5-methylfurfuryldimethylamine boiling at 62–63°/13 mm. is 96–106 g. (69–76%), n_{D}^{25} 1.4616–1.4620.

2. Notes

1. The submitters used du Pont 2-methylfuran. Since the stabilizer contained in this material inhibits the reaction, it should be removed before use. The liquid is stored over solid potassium hydroxide (10 g. for each 100 ml. of 2-methylfuran) for 24 hours, decanted, and stored over the same amount of fresh potassium hydroxide at least overnight. A more rapid but less convenient method of removing the stabilizer is to extract the liquid with 10% aqueous potassium hydroxide until the extracts are only faintly colored.
2. The submitters used commercial sodium hydroxide flakes.
3. The steam distillate amounts to 2–3 l.
4. If a large aqueous phase appears, the amine should be decanted and dried further over a fresh portion of potassium hydroxide pellets.

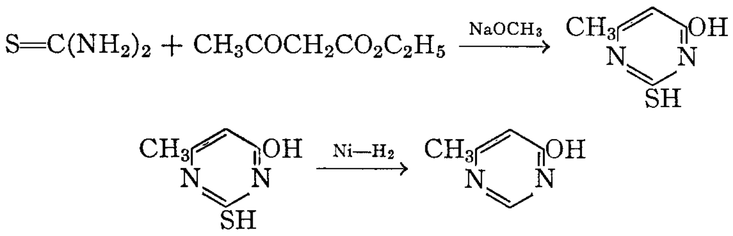
3. Methods of Preparation

The first preparation of 5-methylfurfurylamines by the Mannich reaction was by Holdren and Hixon.[2] The present modification has been published previously[3] without the steam-distillation step, which facilitates separation of the product.

[1] Department of Chemistry, University of Notre Dame, Notre Dame, Indiana.
[2] Holdren and Hixon, *J. Am. Chem. Soc.*, **68**, 1198 (1946).
[3] Eliel and Peckham, *J. Am. Chem. Soc.*, **72**, 1210 (1950).

4-METHYL-6-HYDROXYPYRIMIDINE

(4-Pyrimidinol, 6-methyl-)



Submitted by H. M. FOSTER and H. R. SNYDER.[1]
Checked by R. T. ARNOLD and P. E. THROCKMORTON.

1. Procedure

A. *2-Thio-6-methyluracil.* In a 2-l. flask are placed 76 g. (1 mole) of thiourea, 130 g. (1 mole) of commercial ethyl acetoacetate, 120 g. of commercial sodium methoxide, and 900 ml. of methanol. The reaction mixture is heated gently on the steam bath and is permitted to evaporate to dryness in a hood over a period of about 8 hours. The residue is dissolved in 1 l. of hot water; the solution is treated with a few grams of activated carbon and is filtered. The hot filtrate is carefully treated (Note 1) with 120 ml. of glacial acetic acid. The thiouracil precipitates rapidly and is collected on a 4-in. Büchner funnel. The still wet solid filter cake is suspended in a boiling solution of 1 l. of water and 20 ml. of glacial acetic acid. The slurry is stirred and mixed thoroughly to break up lumps and is then refrigerated.

The product is collected on a 4-in. Büchner funnel and is washed with about 200 ml. of cold water in four portions. The solid is permitted to drain (with suction) for several hours and is then transferred to an oven at 70° for more complete drying. The yield of oven-dried 2-thio-6-methyluracil is 98–119 g. (69–84%). This material is sufficiently pure for the desulfurization reaction (Note 2).

B. *4-Methyl-6-hydroxypyrimidine.* To a hot solution of 10 g. (0.07 mole) of 2-thio-6-methyluracil in 200 ml. of distilled water and 20 ml. of concentrated aqueous ammonia in a 500-ml. round-bottomed flask is added 45 g. (wet paste) of Raney nickel catalyst (Note 3). About 30 ml. of distilled water is used to wash all the nickel catalyst into the reaction flask. The mixture is heated under reflux in a hood for about 1.5 hours. The catalyst is permitted to settle, and the clear solution is decanted and filtered by gravity. The catalyst is washed with two 75-ml. portions of hot water and is discarded (Note 4). The combined filtrate and washings (Note 5) are evaporated to dryness on a steam bath. The residue is placed in an oven at 70° to complete the drying process (Note 6). The yield of crude pyrimidine, m.p. 136–142°, is 7.0–7.2 g. (90–93%).

The crude product is best purified by sublimation under reduced pressure (100–110°/1 mm.) (recovery 90–95%). Purification can also be effected by recrystallization from acetone (recovery 80–90%), ethyl acetate (recovery 70–80%), or ethanol (recovery 60–70%). The purified 4-methyl-6-hydroxypyrimidine melts at 148–149°.

2. Notes

1. The hot solution tends to foam and froth badly when the acetic acid is added, and if care is not taken mechanical loss of product may result.
2. 2-Thio-6-methyluracil does not possess a clearly defined melting point but shows marked decomposition above 280°.[2]
3. The activity of the Raney nickel catalyst greatly affects the yield of the desulfurized pyrimidine. A catalyst described by Brown [3] gave very satisfactory results. A Raney nickel C described by Hurd and Rudner [4] is perhaps a more reactive catalyst; however, the yield of desulfurized pyrimidine was not sufficiently better to warrant its use.
4. Care must be taken not to allow the nickel to dry too completely lest it ignite.
5. The filtrate and washings should be clear and colorless. If the solution is blue or green (indicative of the presence of dis-

solved nickel) the solution should be treated with hydrogen sulfide, or better with dimethylglyoxime and ammonia, to precipitate the nickel.

6. The 4-methyl-6-hydroxypyrimidine is surprisingly volatile, and loss of product may occur if the material is heated on the steam bath for an appreciable period of time.

3. Methods of Preparation

4-Methyl-6-hydroxypyrimidine can be prepared by heating 2,6-dichloro-4-methylpyrimidine with red phosphorus and hydriodic acid [5] and by treating 2-thio-6-methyluracil with hydrogen peroxide.[6] The present synthesis is modeled after the work of Brown,[3] who has described the desulfurization of several thiopyrimidines.

The procedure for the synthesis of 2-thio-6-methyluracil is a modification of the method described by Wheeler and Merriam [7] for the preparation of 2-methylthio-6-methyluracil.

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[1] Department of Chemistry, University of Illinois, Urbana, Illinois.

[2] List, *Ann.*, **236**, 6 (1886).

[3] Brown, *J. Soc. Chem. Ind.* (*London*), **69**, 355 (1950).

[4] Hurd and Rudner, *J. Am. Chem. Soc.*, **73**, 5158 (1951).

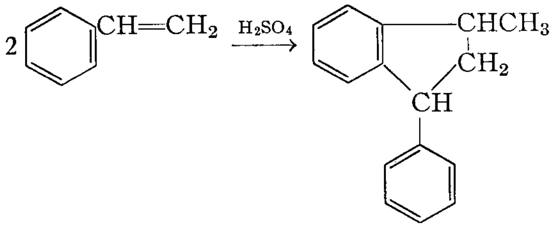
[5] Gabriel and Colman, *Ber.*, **32**, 2931 (1899).

[6] Williams, Ruehle, and Finkelstein, *J. Am. Chem. Soc.*, **59**, 526 (1937).

[7] Wheeler and Merriam, *Am. Chem. J.*, **29**, 486 (1903).

1-METHYL-3-PHENYLINDANE

(1-Methyl-3-phenylindan)



Submitted by Milton J. Rosen.[1]
Checked by R. T. Arnold and William K. Witsiepe.

1. Procedure

In a 500-ml. three-necked round-bottomed flask fitted with a mechanical stirrer and a reflux condenser are placed 50 g. (0.48 mole) of styrene (Note 1) and a previously cooled solution of 100 ml. of concentrated sulfuric acid in 150 ml. of water. The mixture is stirred vigorously (Note 2) and heated under reflux in an oil bath for approximately 4 hours.

Without interrupting stirring or heating, 50 ml. of concentrated sulfuric acid is added slowly through the condenser, and the mixture is stirred and heated for an additional 12 hours (Note 3).

The reaction mixture is cooled, cautiously poured into 250 ml. of cold water with stirring, and allowed to separate into layers. The upper hydrocarbon layer is removed, and the lower layer is extracted with three 50-ml. portions of ether. The combined ether extracts and hydrocarbon layer are washed successively with about 30 ml. each of a saturated solution of sodium bicarbonate, water, and a saturated solution of calcium chloride, and then dried over anhydrous calcium chloride. The ether is removed by distillation, and the product is distilled under reduced pressure. The yield of 1-methyl-3-phenylindane, b.p.

168–169°/16 mm. (Note 4), n_D^{20} 1.5811 ± 0.0005, is 38.5–40.5 g. (77–81%) (Note 5).

2. Notes

1. Commercial styrene, distilled from a water bath at about 80–100 mm. pressure just before use, is employed.

2. It is essential to use an efficient stirring device, capable of forming a dispersion of the styrene in the acid layer.

3. The sulfuric acid is added in two portions in order to minimize higher-polymer formation.[2]

4. The product also distils at 150–151°/6.5 mm.

5. The submitter states that α-methylstyrene can be converted to 1,1,3-trimethyl-3-phenylindane, b.p. 154–155°/8 mm., m.p. 50.4–52.1°, by the same general procedure. The yield is 86–89% of the theoretical amount. The 1,1,3-trimethyl-3-phenylindane may be purified further by one recrystallization from three times its weight of 80% isopropyl alcohol. The yield of purified product, m.p. 51.8–52.3°, is 80–83% (based on the original weight of monomer used).

3. Methods of Preparation

1-Methyl-3-phenylindane can be prepared by treatment of dimeric styrene[3] with aqueous sulfuric acid.

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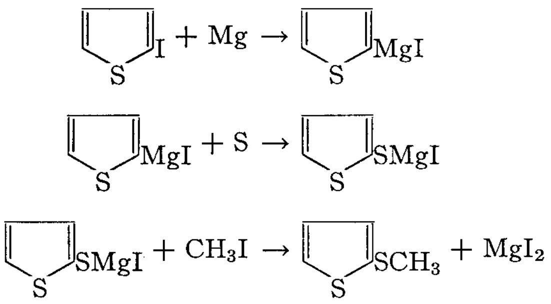
[1] Department of Chemistry, Brooklyn College, Brooklyn, New York.

[2] Rosen, *J. Org. Chem.*, **18**, 1701 (1953).

[3] Spoerri and Rosen, *J. Am. Chem. Soc.*, **72**, 4918 (1950).

METHYL 2-THIENYL SULFIDE

(Sulfide, methyl 2-thienyl)



Submitted by J. Cymerman-Craig and J. W. Loder.[1]
Checked by Charles C. Price and E. A. Dudley.

1. Procedure

In a 1-l. three-necked flask fitted with a liquid-sealed mechanical stirrer, a reflux condenser, and a dropping funnel, are placed 8 g. (0.33 gram atom) of magnesium turnings and 600 ml. of absolute ether. There is placed in the dropping funnel 70 g. (0.33 mole) of 2-iodothiophene,[2] the stirrer is started, and about 10 ml. of the iodothiophene is added. The reaction generally begins within a few minutes (Note 1), and the iodothiophene is then added dropwise at such a rate that moderate refluxing occurs. When the addition is complete, the mixture is refluxed gently until only a small residue of unreacted magnesium remains. The solution is then cooled in an ice bath, the dropping funnel is removed, and 10.7 g. (0.33 gram atom) of finely powdered sulfur (Note 2) is added (Note 3), the funnel is replaced, and the mixture is refluxed (Note 4) for 45 minutes. The solution is again cooled in an ice bath, and 22.6 ml. (0.36 mole) of methyl iodide is added dropwise from the funnel, and the stirring is then discontinued (Note 5). The reaction mixture is refluxed 10 hours. It is then cooled, and an aqueous solution of ammonium chloride is run in with vigorous stirring (Note 6). The liquid is transferred to a separatory funnel, the lower aqueous layer is run off, and the ethereal solution is washed three times with a 2% solution of potassium hydroxide, then with water, and finally is dried over anhydrous sodium sulfate. The ether is removed by distillation at ordinary pressure, and the residual dark liquid is distilled under reduced pressure. The yield of colorless methyl 2-thienyl sulfide is 23–26 g. (52–60%), b.p. 82–86°/22 mm., n_D^{25} 1.5978 (Notes 7 and 8).

2. Notes

1. If the reaction does not start, it may be assisted by the addition of a small amount of methylmagnesium iodide in ethereal solution.
2. The sulfur was distilled and then ground in a mortar before use.
3. The mechanical stirring is continued. The sulfur dissolves during the refluxing period to give a clear yellow solution. A sludge which adheres to the bottom of the flask may form, but the yield is unaltered.
4. On reheating, a vigorous reaction with the sulfur occurs. A means of cooling the reaction flask should be at hand to ensure control of the reaction.
5. The solution may be left overnight at this stage, sealed under nitrogen.
6. The decomposition of the unreacted Grignard reagent is best carried out in a hood to remove the strong odor of thiols.
7. Considerable decomposition occurs if distillation is attempted at atmospheric pressure. The product is sometimes pale yellow, and darkens slightly on standing.
8. A dark oil remains which decomposes at this pressure when strongly heated.

3. Methods of Preparation

Methyl 2-thienyl sulfide has been prepared by the action of phosphorus trisulfide on dimethyl succinate [3] and by the action

of methyl iodide on the sodium salt of 2-thiophenethiol,[4] both of which methods are of little preparative value. The procedure described above is that of Cymerman-Craig and Loder.[5]

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[1] University of Sydney, Sydney, Australia.

[2] *Org. Syntheses* Coll. Vol. **2**, 357 (1943); *Org. Syntheses*, **30**, 53 (1950).

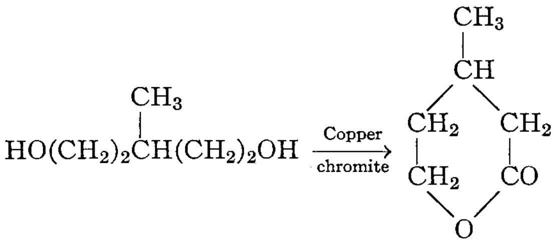
[3] Steinkopf and Leonhardt, *Ann.*, **495**, 166 (1932).

[4] Meyer and Neure, *Ber.*, **20**, 1756 (1887).

[5] Cymerman-Craig and Loder, *J. Chem. Soc.*, **1954**, 241.

β-METHYL-δ-VALEROLACTONE

(Valeric acid, 5-hydroxy-3-methyl-, δ-lactone)



Submitted by Raymond I. Longley, Jr., and William S. Emerson.[1]
Checked by T. L. Cairns and W. W. Gilbert.

1. Procedure

A 1-l. three-necked flask fitted with an efficient stirrer, a thermometer, and a reflux condenser attached to a device for measuring gas evolution (Note 1) is charged with 197 g. (1.67 moles) of 3-methyl-1,5-pentanediol [2] and 10 g. of copper chromite (Note 2). The mixture is heated rapidly to 200° (Note 3) with good stirring, and is held at 195–205° for 1.5–3.0 hours, during which time 3.1 cu. ft. of hydrogen is evolved (Note 4). The product is distilled directly from the flask with stirring through a 2 by 120 cm. Vigreux column (Note 5). The yield of β-methyl-δ-valerolactone is 172–180 g. (90–95%), b.p. 110–111°/15 mm., n_D^{25} 1.4495.

2. Notes

1. A standard wet test meter may be used.
2. Copper chromite is prepared according to *Organic Syntheses*[3] and washed with sodium bicarbonate solution. The glycol is slurried with sodium bicarbonate and filtered before use.
3. At this point gas evolution becomes so rapid that the temperature tends to drop slightly.
4. If gas evolution subsides more catalyst may be added.
5. The column is substituted for the reflux condenser in the same set-up. Stirring during distillation prevents serious bumping.

3. Methods of Preparation

β-Methyl-δ-valerolactone has been prepared by heating 3-methyl-1,5-pentanediol with copper chromite in the liquid phase,[4] by passing the vapors of 3-methyl-1,5-pentanediol over copper on pumice,[4] by heating 2-methoxy-4-methyl-3,4-dihydro-2H-pyran with water and copper chromite,[4] by treating 3-methylglutaraldehyde with aqueous alkali,[4] and by reducing β-methylglutaric anhydride with sodium and ethanol.[5] The present method was first developed by Kyrides and Zienty.[6]

[1] Central Research Department, Monsanto Chemical Company, Dayton 7, Ohio.

[2] *Org. Syntheses*, **34**, 71 (1954).

[3] *Org. Syntheses* Coll. Vol. **2**, 142 (1943).

[4] Longley, Emerson, and Shafer, *J. Am. Chem. Soc.*, **74**, 2012 (1952).

[5] Sircar, *J. Chem. Soc.*, **1928**, 898.

[6] Kyrides and Zienty, *J. Am. Chem. Soc.*, **68**, 1385 (1946).

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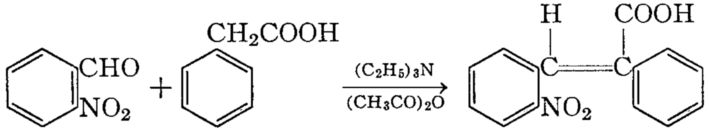
trans-o-NITRO-α-PHENYLCINNAMIC ACID

[Acrylic acid, *trans*-β-(*o*-nitrophenyl)-α-phenyl-]



Submitted by DeLos F. DeTar.[1]
Checked by Charles C. Price and J. D. Berman.

1. Procedure

A mixture of 30.2 g. (0.20 mole) of *o*-nitrobenzaldehyde,[2] 40 g. (0.29 mole) of phenylacetic acid, 100 ml. (1.08 moles) of acetic anhydride, and 20 g. (0.20 mole) of triethylamine is refluxed for 15 minutes in a 500-ml. flask. The solution is cooled to 90°, and 100 ml. of cold water is added over a 5-minute period at a rate that maintains the temperature above 90° (Note 1). The solution is filtered at 95–100° and cooled to 20°. *trans-o*-Nitro-α-phenylcinnamic acid precipitates in the form of light-orange crystals. It is separated by filtration and washed with 60 ml. of 50% acetic acid and with water. The dried acid weighs 39–42 g. (72–77%) and melts at 195–198°, which corresponds to a purity of about 98% (Note 2). After recrystallization from 500 ml. of toluene, it is in the form of yellow prisms weighing 38–39 g. (71–72%) and melting at 197.8–198.3°.

2. Notes

1. If the temperature gets too high, more cold water may be added. If the water is added too rapidly at first, the temperature drops below 90° and the rate of hydrolysis becomes very slow. Heating such an incompletely hydrolyzed mixture above 90° may cause it to boil violently.

2. Approximate melting points of mixtures of the *trans*- and *cis*-*o*-nitro-α-phenylcinnamic acids are as follows:

Per Cent *cis*	Sinter Point	Melting Point, °C.
33		134–185
23	130	136–187
13	131	165–192
8	135	184–196
3.5	140	192–198
1.5	170	195–198
—	196	197.8–198.3

3. Methods of Preparation

trans-*o*-Nitro-α-phenylcinnamic acid has been prepared by the condensation of *o*-nitrobenzaldehyde with sodium phenylacetate in the presence of acetic anhydride with[3] or without[4] fused zinc chloride as a catalyst. It has also been prepared by the condensation of *o*-nitrobenzaldehyde with phenylacetic acid in the presence of acetic anhydride and triethylamine.[5]

[1] University of South Carolina, Columbia, South Carolina.

[2] *Org. Syntheses* Coll. Vol. **3**, 641 (1955).

[3] Pschorr, *Ber.*, **29**, 496 (1986).

[4] Oglialoro and Rosini, *Gazz. chim. ital.*, **20**, 396 (1890).

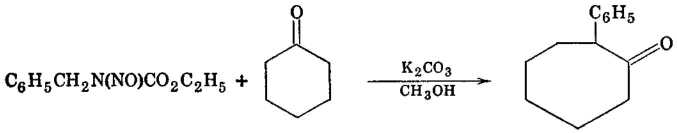
[5] Bakunin and Peccerillo, *Gazz. chim. ital.*, **65**, 1145 (1935).

2-PHENYLCYCLOHEPTANONE

(Cycloheptanone, 2-phenyl-)

$$C_6H_5CH_2NH_2 + ClCO_2C_2H_5 + NaOH \longrightarrow C_6H_5CH_2NHCO_2C_2H_5 + NaCl + H_2O$$

$$C_6H_5CH_2NHCO_2C_2H_5 + NaNO_2 + HNO_3 \longrightarrow C_6H_5CH_2N(NO)CO_2C_2H_5 + NaNO_3 + H_2O$$



Submitted by C. David Gutsche and Herbert E. Johnson.[1]
Checked by N. J. Leonard and F. P. Hauck, Jr.

1. Procedure

A. *Ethyl N-benzylcarbamate.* A 12-l. three-necked flask fitted with a sturdy Hershberg-type stirrer and two 1-l. addition funnels is immersed in an ice bath and charged with 1 kg. (9.33 moles) of benzylamine, 500 ml. of ice water, and 1.5 kg. of chopped ice. To the stirred mixture 525 g. (4.83 moles) of ethyl chlorocarbonate is added dropwise while the temperature is maintained at 10–15° (1.0–1.5 hours) (Note 1). An additional 500 ml. of water and 1 kg. of chopped ice are then added to the flask, and a second 525-g. portion (4.83 moles) of ethyl chlorocarbonate is introduced. Simultaneously with this, an ice-cold solution of 400 g. (10 moles) of sodium hydroxide in 1.3 l. of water is added dropwise at such a rate that equal fractions of the ethyl chlorocarbonate and sodium hydroxide solutions are introduced over equal periods of time, the temperature being maintained throughout at 10–15° (2.5–3.0 hours). The reaction mixture is stirred for an additional 30 minutes and is then filtered through a Büchner funnel. The solid product is washed with copious amounts of cold water and is air-dried to yield 1.6 kg. (96%) of glistening white crystals, m.p. 45–47°.

B. *Ethyl N-nitroso-N-benzylcarbamate* (Note 2). In a 12-l. three-necked flask fitted with a thermometer, a 2-l. addition funnel (Note 3), and a gas outlet tube are placed a solution of 360 g. (2.0 moles) of ethyl N-benzylcarbamate in 2 l. of ether and a solution of 1.2 kg. (17.4 moles) of sodium nitrite in 2 l. of water. A stirrer is not used. The reaction mixture is cooled by means of a water bath to 20° and treated with a solution of 1 l. each of concentrated nitric acid and water, contained in the addition funnel. Enough of this solution is added to impart a permanent green color to the aqueous layer, and the remainder is then added over a period of 5 hours at such a rate as to keep the aqueous phase green (Note 4) and the temperature at 25–30°. The reaction mixture is allowed to stand an additional 30 minutes, and the layers are separated. The ether layer is washed with 200-ml. portions of 10% potassium carbonate solution (Note 5) until the evolution of gas ceases and is then dried over anhydrous potassium carbonate. The ether is removed under vacuum on a water bath kept below 50° (Note 6), a residue of 400–415 g. (95–100%) of a bright orange oil (Note 7) being left.

C. *2-Phenylcycloheptanone.* In a 2-l. three-necked flask fitted with a 500-ml. addition funnel, a sealed Hershberg stirrer, and a reflux condenser (Note 8) are placed 392 g. (4.0 moles) of freshly distilled cyclohexanone, 30 g. of finely powdered potassium carbonate, and 400 ml. of absolute methanol. To the stirred mixture is added 415 g. (2.0 moles) of ethyl N-nitroso-N-benzylcarbamate over a period of 1.5 hours during which time the reaction temperature is maintained at 25° by means of an ice-water bath. The dark red reaction mixture is then allowed to stand at room temperature until the evolution of nitrogen has ceased (24–28 hours) (Note 9). The solid material is removed by filtration, the lower-boiling materials are removed by evaporation under reduced pressure on the steam bath (Note 10), and the residue is distilled through an efficient column. A fore-run consisting of 30–60 g. of material is discarded or refractionated (Note 10), and the fraction with b.p. 94–96°/0.4 mm. (124–126°/2 mm., 136–138°/4 mm.) is collected. It amounts to 155–177 g. (40–47%) of 2-phenylcycloheptanone, n_D^{20} 1.5395–1.5398, which is pure enough for most purposes, but which may be purified further by recrystallization from petroleum ether (b.p. 30–60°) and obtained as colorless, very long needles; m.p. 21–23° (Note 11).

2. Notes

1. During this time ethyl N-benzylcarbamate begins to separate from solution as a white solid.

2. Although the benzyl nitroso compound appears to be a much less active vesicant than the methyl nitroso compound, it is, nevertheless, a wise precaution to wear heavy rubber gloves during the isolation of this product.

3. The stem of the addition funnel should reach to the bottom of the flask.

4. The color may appear yellow green, emerald green, or blue-green, depending upon the size of the run, the amount of nitric acid that has been added, and the room lighting.

5. Seven to nine portions of carbonate solution are sufficient if each portion is shaken very thoroughly with the ether solution. Caution should be observed because of pressure build-up in the separatory funnel!

6. Ethyl N-nitroso-N-benzylcarbamate is heat sensitive and, if the temperature is too high, *may detonate violently*. The submitters state that attempts to distil the nitroso compound under high vacuum have resulted in explosions.

7. The submitters state that the nitroso compound is stable at low temperature and can be stored in a refrigerator for several months or longer with no signs of deterioration.

8. The reflux condenser is an optional but convenient appendage for the third neck of the flask. To follow the evolution of nitrogen during the reaction, the exit from the condenser can be led either to a eudiometer tube (theoretical nitrogen evolution about 50 l. for the experiment described) or to a bubbler.

9. It is necessary to allow the reaction mixture to stand for a rather prolonged period, since about 40% of the nitrogen is evolved during this time.

10. The lower-boiling material includes methyl benzyl ether,

which may be isolated, by careful fractionation through an efficient column, in about 25% yield, b.p. 74–77°/30 mm.

11. In a similar fashion the following 2-arylcycloheptanones have been prepared by the submitters:

	Yield, %	Melting Point or Refractive Index at 25°
2-(*o*-Methylphenyl)cycloheptanone	29	1.5348
2-(*p*-Methylphenyl)cycloheptanone	26	57–58°
2-(*o*-Methoxyphenyl)cycloheptanone	7	1.5407
2-(*m*-Methoxyphenyl)cycloheptanone	42	1.5418
2-(*p*-Methoxyphenyl)cycloheptanone	20	58–59°

3. Methods of Preparation

Ethyl N-benzylcarbamate and its nitroso compound have been prepared by methods similar to those described for ethyl N-methylcarbamate and its nitroso compound.[2,3] 2-Phenylcycloheptanone has been prepared by the reaction of ethyl N-nitroso-N-benzylcarbamate[4] with cyclohexanone,[5] by the reaction of phenyldiazomethane with cyclohexanone,[6] by the reaction of ethyl N-nitroso-N-methylcarbamate with 2-phenylcyclohexanone,[5] and by the rearrangement of 1-phenyl-2-cyclohexylethylene oxide.[7]

[1] Washington University, St. Louis, Missouri.

[2] *Org. Syntheses* Coll. Vol. **2**, 278 (1943).

[3] *Org. Syntheses* Coll. Vol. **2**, 464 (1943).

[4] v. Pechmann, *Ber.*, **31**, 2640 (1898).

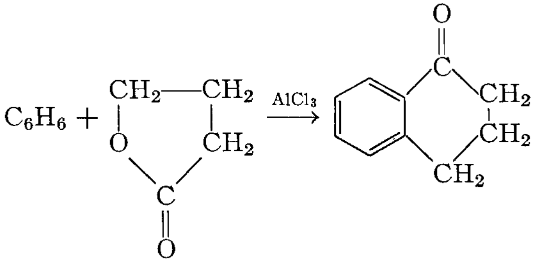
[5] Gutsche, *J. Am. Chem. Soc.*, **71**, 3513 (1949).

[6] Burger, Walter, Bennet, and Turnbull, *Science*, **112**, 306 (1950).

[7] Tiffeneau, Weill, Gutman, and Tchoubar, *Compt. rend.*, **201**, 277 (1935).

1-TETRALONE

[1(2H)-Naphthalenone, 3,4-dihydro-]



Submitted by Cecil E. Olson and Alfred R. Bader.[1]
Checked by James Cason, Gerhard J. Fonken, and William G. Dauben.

1. Procedure

A 3-l. three-necked flask is fitted with a mercury-sealed stirrer, an efficient condenser capped by a drying tube filled with calcium chloride, and a wide-bore rubber tube leading to a 1-l. Erlenmeyer flask. One liter of dry, thiophene-free benzene and 104 g. (1.21 moles) of γ-butyrolactone (Note 1) are placed in the 3-l. flask. Six hundred grams (4.5 moles) of reagent-grade anhydrous aluminum chloride (Note 2) is placed in the Erlenmeyer flask and is added to the stirred reaction mixture during a period of 2 hours. The mixture becomes dark brown, refluxes gently, and evolves hydrogen chloride. After addition of all the catalyst, the mixture is heated on a steam bath with continued stirring for 16 hours. It is then cooled to room temperature and poured onto 3 kg. of crushed ice drenched with 500 ml. of concentrated hydrochloric acid. The lower aqueous layer is separated and extracted with about 500 ml. of toluene. The brown, organic, upper layer and the toluene extract are combined, washed successively with water, 20% potassium hydroxide solution, and water, and distilled under reduced pressure to remove benzene, toluene, and traces of water. Distillation of the residue in a Claisen flask (Note 3) yields 160–

170 g. (91–96%) of 1-tetralone, b.p. 75–85°/0.3 mm., n_{D}^{25} 1.565–1.568 (Notes 4 and 5). There is a residue consisting of 130–150 g. of red-purple viscous oil.

2. Notes

1. A commercial grade of butyrolactone supplied by the General Aniline and Film Corporation, 230 Park Avenue, New York 17, New York, was used by the submitters. The checkers used material from Eastern Chemical Corporation, 34 Spring Street, Newark 2, New Jersey, which was distilled before use, b.p. 208–210°.

2. The checkers found technical aluminum chloride, containing a little ferric chloride, equally satisfactory. After 150–200 g. of aluminum chloride is added there is usually a rather sudden and vigorous evolution of hydrogen chloride accompanied by refluxing. It is advisable to interrupt addition of aluminum chloride at this point until the mixture is refluxing smoothly.

3. The checkers distilled the product through a 0.5-meter packed column with heated jacket and partial reflux head. The yield was 148–155 g. (85–88%), b.p. 143–145°/20 mm., n_{D}^{25} 1.5669–1.5671. There was a fore-run of 10–15 g. and an after-run of about 8 g., b.p. 145–180°/20 mm.

4. The submitters state that varying the amounts of aluminum chloride varied the yields as follows:

$AlCl_3$, grams	1-Tetralone, grams	Yield, %
400	119	68
500	151	86
600	165	94
700	166	95

5. Replacing the butyrolactone with 120 g. (1.20 moles) of γ-valerolactone in an otherwise identical procedure yields 150–160 g. (79–84%) of 4-methyl-1-tetralone, b.p. 108–110°/1 mm.

3. Methods of Preparation

1-Tetralone has been prepared by cyclization of γ-phenylbutyryl chloride by aluminum chloride[2] or stannic chloride;[3] from γ-phenylbutyric acid and a mixture of phosphorus pentoxide and phosphoric acid;[4] from tetrahydronaphthalene peroxide and sodium hydroxide[5] or cupric chloride;[6] and from benzene, γ-butyrolactone, and aluminum chloride.[7] Other methods of preparation have been reviewed in earlier volumes.[2,5] The above is based on the method of Truce and Olson.[7]

4-Methyl-1-tetralone has been prepared from γ-phenylvaleric acid and sulfuric acid[8] and from γ-phenylvaleryl chloride and aluminum chloride.[9,10] Its preparation from γ-valerolactone has not been described elsewhere.

---

[1] Pittsburgh Plate Glass Company, Milwaukee 1, Wisconsin.

[2] *Org. Syntheses* Coll. Vol. **2**, 570 (1943).

[3] *Org. Syntheses*, **33**, 90 (1953).

[4] Birch, Jaeger, and Robinson, *J. Chem. Soc.*, **1945**, 586.

[5] *Org. Syntheses* Coll. Vol. **3**, 798 (1955).

[6] Johnson, U. S. pat. 2,462,103 [*C. A.*, **43**, 3848 (1949)].

[7] Truce and Olson, *J. Am. Chem. Soc.*, **74**, 4721 (1952).

[8] Kloetzel, *J. Am. Chem. Soc.*, **62**, 1708 (1940).

[9] Mayer and Stamm, *Ber.*, **56**, 1431 (1923).

[10] v. Braun and Stuckenschmidt, *Ber.*, **56**, 1724 (1923).

THIOBENZOPHENONE

(Benzophenone, thio-)

$$(C_6H_5)_2CO + H_2S \xrightarrow{HCl} (C_6H_5)_2CS + H_2O$$

Submitted by B. F. GOFTON and E. A. BRAUDE.[1]
Checked by CHARLES C. PRICE and J. FRANK GILLESPIE.

1. Procedure

Caution! This preparation should be conducted in a good hood.

A 250-ml. three-necked flask is equipped with a rubber-sealed mechanical stirrer, two gas-inlet tubes, and a mercury-sealed escape valve consisting of an outlet tube dipping into a test tube of mercury. A solution of 25 g. (0.14 mole) of benzophenone in 125 ml. of 95% ethanol is placed in the flask, which is cooled in an ice-salt freezing mixture. Hydrogen sulfide and hydrogen chloride are passed simultaneously into the stirred solution for 3 hours (Note 1). Within 1 hour the solution becomes blue. After 3 hours, the flow of hydrogen chloride is stopped and hydrogen sulfide alone is passed for a further 20 hours, with continued ice cooling. Toward the end of the reaction, the contents of the flask assume an intense violet color. The solid thiobenzophenone (23–25 g.) is filtered from the ice-cold solution in an atmosphere of carbon dioxide (Note 2), immediately dried under high vacuum (Note 3), and recrystallized twice from about 20 ml. of petroleum ether (b.p. 60–80°), giving long needles, m.p. 53–54°. The yield of purified product is 18–21 g. (66–77%).

2. Notes

1. Hydrogen chloride was generated by dropping concentrated sulfuric acid on ammonium chloride. Hydrogen sulfide was generated in a Kipp's apparatus from iron sulfide and hydrochloric acid. (The checkers used tank hydrogen sulfide.)

2. A convenient filtration apparatus for this purpose may be constructed by cutting the bottom off a bottle and then inserting a Büchner funnel through a stopper in the mouth of the bottle. The space between the bottle and the funnel is then packed with Dry Ice.

3. It has been found essential to dry the crude material immediately after filtration; otherwise it changes into a blue oil after standing for a few hours.

3. Methods of Preparation

The method described here is adapted from the procedure of Staudinger and Freudenberger.[2] It has been found to be more convenient and to give more reproducible results than the two-stage procedure given in *Organic Syntheses*,[3] where references to other methods of preparation are also cited.

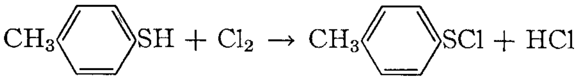
---

[1] Imperial College of Science and Technology, London, England.

[2] Staudinger and Freudenberger, *Ber.*, **61**, 1577 (1928).

[3] *Org. Syntheses* Coll. Vol. **2**, 574 (1943).

p-TOLUENESULFENYL CHLORIDE



$CH_3C_6H_4SH + Cl_2 \rightarrow CH_3C_6H_4SCl + HCl$

Submitted by FREDERICK KURZER and J. ROY POWELL.[1]
Checked by RICHARD S. SCHREIBER and FRED KAGAN.

1. Procedure

Caution! This preparation should be conducted in a good hood.

Chlorine (Note 1) is passed into 300 ml. of anhydrous carbon tetrachloride (Note 2) contained in a 500-ml. three-necked round-bottomed flask equipped with a mechanical stirrer, a dropping funnel protected from atmospheric moisture by a calcium chloride tube, and a gas-inlet tube equipped with a sintered-glass tip (Note 3). The amount of chlorine contained in the resulting yellow-green liquid, estimated volumetrically (Note 4), varies between 25 and 32 g. The gas-inlet tube is replaced by a calcium chloride tube, and the reaction vessel is cooled externally with ice water and protected from light by being covered with a towel.

One or two crystals of iodine are added to the chlorine solution, and a solution of *p*-toluenethiol (7.3 g. per 10 g. of dissolved chlorine, i.e., halogen in 140% excess) (Note 5) in 50 ml. of anhydrous carbon tetrachloride (Note 2) is added dropwise over a period of approximately 1 hour. The initial slight turbidity disappears gradually, a bright orange solution being formed (Note 6). After an additional 30 minutes' stirring, the solvent and excess chlorine are rapidly removed under reduced pressure at the lowest possible temperature (Note 7), the crude sulfenyl chloride being left as an orange-red mobile liquid (Note 8). For batches starting with 24.8 g. (0.2 mole) of *p*-toluenethiol, the yield varies between 27 and 30.5 g. (85–96%).

Rapid distillation under reduced pressure affords *p*-toluenesulfenyl chloride as a red mobile liquid boiling at 66–68°/0.8 mm.

(74–76°/1.5 mm.; 82–84°/3.5 mm.) (Note 9). The yield of redistilled material varies between 24.5 and 28 g. (77–88%).

2. Notes

1. The checkers used tank chlorine obtained from the Ohio Chemical and Surgical Equipment Company, Detroit, Michigan. The gas was dried with concentrated sulfuric acid and used with no further purification. The rate of chlorine addition was regulated so that no chlorine escaped from the carbon tetrachloride solution. After 1.5–2.0 hours, 27–33 g. of chlorine was absorbed. The submitters generated chlorine by the action of concentrated hydrochloric acid on potassium permanganate.

2. The carbon tetrachloride is treated with a small quantity of phosphorus pentoxide, and the suspension is set aside for 1–2 hours. The clear supernatant liquid is first decanted into a dry flask and gently shaken. Any droplets of phosphoric acid are retained on the walls of this vessel; the anhydrous solvent is then easily decanted.

3. During the slow absorption of chlorine, the solution is satisfactorily protected from atmospheric moisture by means of a plug of cotton wool through which the gas-inlet tube passes. The temperature of the solution does not rise, and external cooling is not required.

4. A 2-ml. aliquot of the solution, withdrawn by means of a safety pipet, is added to 20 ml. of water containing 2 g. of potassium iodide, and the liberated iodine is titrated with good shaking with standard sodium thiosulfate solution.

5. When a smaller excess of chlorine is used poorer yields of sulfenyl chloride are obtained, a larger proportion of *p*-tolyl disulfide being formed.

6. The checkers found that the turbidity persisted throughout the addition of the *p*-toluenethiol and that a small amount of an orange-yellow solid was present at the end of the addition. This material dissolved during the concentration under reduced pressure.

7. Since traces of sulfenyl chloride are carried over with the carbon tetrachloride, the distillate varies from light to deep yellow during the concentration. Recovery of this material by repeated distillation is not economical.

8. This material is suitable for use in further synthesis without purification by distillation, particularly if the presence of a few per cent of *p*-tolyl disulfide is of no consequence.

9. The checkers found that 76% of the product boiled at 64–66°/1.1 mm. and 24% boiled at 66–74°/1.1 mm.; however, the index of refraction of the two fractions was constant (n_D^{20} 1.6018–1.6019). As the first few drops of distillate were green, they were discarded.

3. Methods of Preparation

p-Toluenesulfenyl chloride has been prepared by the action of chlorine on a solution of *p*-toluenethiol or *p*-tolyl disulfide in anhydrous carbon tetrachloride.[2,3] Benzenesulfenyl chloride has also been obtained by the interaction of hydrogen chloride and N,N-diethylbenzenesulfenamide [4] and by reaction of benzenethiol with N-chlorosuccinimide.[5] A comprehensive review dealing with sulfenyl halides and related compounds is available.[6]

---

[1] University of London, London, England.

[2] Lecher, Holschneider, Koberle, Speer, and Stocklin, *Ber.*, **58**, 409 (1925).

[3] Lecher and Holschneider, Ger. pat. 423,232 (*Brit. C. A.*, **1926**, B, 386).

[4] Lecher and Holschneider, *Ber.*, **57**, 755 (1924).

[5] Emde, Ger. pat. 804,572 [*C. A.*, **46**, 529 (1952)].

[6] Kharasch, Potempa, and Wehrmeister, *Chem. Revs.*, **39**, 269 (1946).

SUBJECT INDEX

(This cumulative index comprises material from Volumes 30, 31, 32, 33, 34, and 35; for previous volumes see Collective Volumes 1, 2, and 3.)

Names in small capital letters refer to the titles of individual preparations. A number in ordinary bold-face type denotes the volume. A page number in bold-face italics indicates that the detailed preparative directions are given or referred to; entries so treated include principal products and major by-products, special reagents or intermediates (which may or may not be isolated), compounds mentioned in the text or Notes as having been prepared by the method given, and apparatus described in detail or illustrated by a figure. Page numbers in ordinary type indicate pages on which a compound or subject is mentioned in connection with other preparations. For example, Allylbenzene, **31**, 85, ***86***, indicates that allylbenzene is mentioned on page 85, and that directions for its preparation are given on page 86, of Volume 31.

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