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. The submitter should provide substantial reasons why his procedure merits consideration for inclusion in *Organic Syntheses*, e.g., novelty, general applicability, or potential wide interest in the method or the specific product.

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 the preparations previously published are welcomed and should be sent to the Secretary.

BISCHLOROMETHYL ETHER

[Ether, bis(chloromethyl)-]

$$2CH_2O + 2HCl \rightarrow ClCH_2OCH_2Cl + H_2O$$

$$2CH_2O + 2ClSO_3H + H_2O \rightarrow ClCH_2OCH_2Cl + 2H_2SO_4$$

Submitted by Saul R. Buc.[1]
Checked by Charles C. Price, Frederick V. Brutcher, and Jerome Cohen.

1. Procedure

Caution! Bischloromethyl ether is a mild lachrymator. Appropriate precautions should be taken.

In a 1-l. three-necked flask immersed in an ice bath and provided with a stirrer, thermometer, and dropping funnel are placed 168 ml. (200 g.) of concentrated (37–38%) hydrochloric acid (2 moles) and 240 g. of paraformaldehyde (effectively 8 moles of formaldehyde). While the temperature is maintained below 10°, 452 ml. (6.9 moles) of chlorosulfonic acid is added dropwise at such a rate that gaseous hydrogen chloride is not lost from the mixture. This requires about 5.5 hours. The mixture is stirred for 4 hours in the melting ice bath and comes to room temperature. It may be allowed to stand overnight. The layers are separated, and the product (upper layer) is washed twice with ice water. Ice is added to the product, and 250 ml. of 40% sodium hydroxide is then added to the mixture slowly with vigorous agitation until the aqueous phase is strongly alkaline (Note 1). The product is separated and dried rapidly over potassium carbonate and then over potassium hydroxide, keeping the product cold during drying (Note 2). After separation of the drying agent by filtration, 350–370 g. (76–81%) of product sufficiently pure for many purposes is obtained. On distillation there is obtained 330–350 g. (72–76%) of bischloromethyl ether, boiling at 100–104°. Approximately 95% boils at 101–101.5°, n_D^{25} 1.4420 (Note 3).

2. Notes

1. Local overheating must be carefully avoided during the alkaline washing, since it may result in vigorous decomposition.

2. The washing and drying are carried out as rapidly as possible to avoid hydrolysis of the product.

3. The submitter reports that operation of this procedure on a scale of 72 moles of paraformaldehyde gave a crude yield of 3601 g. (87%) and a distilled yield of 3519 g. (85%).

3. Methods of Preparation

Bischloromethyl ether has been prepared by saturation of formalin with dry hydrogen chloride,[2,3,4] by the reaction of paraformaldehyde with phosphorus trichloride[5,6] or phosphorus oxychloride,[7,8] by solution of paraformaldehyde in concentrated sulfuric acid and treatment with ammonium chloride or dry hydrogen chloride,[9] and by suspension of paraformaldehyde in seventy[10] or eighty[11] percent sulfuric acid and treatment with chlorosulfonic acid. It is formed together with the asymmetrical isomer when methyl ether is chlorinated[12] and when paraformaldehyde is treated with chlorosulfonic acid.[13] The present method has been published.[14]

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[1] Central Research Laboratory, General Aniline and Film Corporation, Easton, Pennsylvania.

[2] Tishchenko, *Zhur. Russ. Fiz. Khim. Obshchestva*, **19**, 464 (1887); *Ber.*, **20**, 701 (1887).

[3] Litterscheid and Thimme, *Ann.*, **334**, 1 (1904).

[4] Stephen, Short, and Gladding, *J. Chem. Soc.*, **117**, 510 (1920).

[5] Descudé, *Bull. soc. chim. Paris*, [3], **35**, 953 (1906).

[6] Beeby and Mann, *J. Chem. Soc.*, **1949**, 1799.

[7] Löbering and Fleischmann, *Ber.*, **70B**, 1680 (1937).

[8] Backès, *Bull. soc. chim. France*, [5], **9**, 60 (1942).

[9] Schneider, *Z. angew. Chem.*, **51**, 274 (1938).

[10] Norris, *Ind. Eng. Chem.*, **11**, 827 (1919).

[11] Vorozhtzov and Yuruigina, *Zhur. Obshcheĭ Khim.*, **1**, 49 (1931) [*C. A.*, **25**, 4521 (1931)].

[12] Salzberg and Werntz (to E. I. duPont de Nemours and Company), U. S. pat. 2,065,400 [*C. A.*, **31**, 1046 (1937)].

[13] Fuchs and Katscher, *Ber.*, **60B**, 2288 (1927).

[14] Buc (to General Aniline and Film Corporation), U. S. pat. 2,704,299 [*C. A.*, **50**, 1891 (1956)].

α-CHLOROPHENYLACETIC ACID

(Acetic acid, α-chlorophenyl-)

$$C_6H_5CHOHCO_2H + C_2H_5OH \xrightarrow{HCl} C_6H_5CHOHCO_2C_2H_5$$

$$C_6H_5CHOHCO_2C_2H_5 + SOCl_2 \rightarrow C_6H_5CHClCO_2C_2H_5 + HCl + SO_2$$

$$C_6H_5CHClCO_2C_2H_5 + CH_3CO_2H \xrightarrow{HCl} C_6H_5CHClCO_2H + CH_3CO_2C_2H_5$$

Submitted by Ernest L. Eliel, Milton T. Fisk, and Thomas Prosser.[1]
Checked by James Cason, Lois J. Durham, and Gerhard J. Fonken.

1. Procedure

A. *Ethyl mandelate.* To 152 g. (1.0 mole) of mandelic acid and 200 ml. of absolute ethanol in a 1-l. round-bottomed flask equipped with a reflux condenser, there is added 100 ml. of absolute ethanol containing about 10 g. of anhydrous hydrogen chloride (Note 1). The solution is heated under reflux on a steam bath for 5 hours, then poured into 1 l. of ice water in a 3-l. beaker (Note 2). A saturated aqueous solution of sodium bicarbonate is added until the mixture is faintly alkaline (Note 3). It is then extracted with two 300-ml. portions of ether in a 2-l. separatory funnel. The ether extracts are washed with a 200-ml. portion of water and dried over 50 g. of anhydrous sodium sulfate. The dried ether solution is concentrated by distillation from a 250-ml. Claisen flask, and the residue is distilled at reduced pressure. There is obtained 147–154 g. (82–86%) of ethyl mandelate, b.p. 144–145°/16 mm. The ester may crystallize upon standing for a prolonged period. It melts at 30.5–31.5°.

B. *Ethyl α-chlorophenylacetate.* Ethyl mandelate (135 g., 0.75 mole) is dissolved in 98 g. (59 ml., 0.82 mole) of thionyl chloride (Note 4) contained in a 500-ml. round-bottomed flask equipped with a reflux condenser capped with a drying tube. The apparatus is allowed to stand in a hood overnight (about 16 hours), at the end of which time the solution is heated under reflux for

30 minutes on a steam bath. The solution is then poured into 750 ml. of ice water contained in a 2-l. separatory funnel (Note 5), and the mixture is extracted with two 300-ml. portions of ether. The combined ether extracts are washed with two 250-ml. portions of saturated aqueous sodium bicarbonate solution and one 250-ml. portion of water. The washed extracts are dried over 45 g. of anhydrous sodium sulfate and concentrated by distillation. The residue is distilled from a 250-ml. Claisen flask at reduced pressure. The yield of ethyl α-chlorophenylacetate is 121–127 g. (81–85%), b.p. 134–136°/15 mm., n_D^{20} 1.5149.

C. *α-Chlorophenylacetic acid.* A solution of 119 g. (0.6 mole) of ethyl α-chlorophenylacetate in 238 ml. of glacial acetic acid and 119 ml. of concentrated hydrochloric acid, contained in a 1-l. round-bottomed flask, is heated under reflux in a hood for 1.5 hours (Note 6). At the end of the heating period the solution is concentrated by heating in an oil bath at 100° at reduced pressure (15–20 mm.) until no further material is distilled (Note 7). The residue is allowed to cool to room temperature and poured slowly, with stirring, into 1-l. of ice-cold saturated sodium bicarbonate solution contained in a 2-l. beaker. Solid sodium bicarbonate is added in small portions until the solution becomes neutral to universal indicator paper (Note 8). The solution is then extracted with two 200-ml. portions of ether in a 2-l. separatory funnel (Notes 9, 10). The aqueous phase is placed in a 3-l. beaker and acidified cautiously with ice-cold 12 *N* sulfuric acid until the mixture is acid to Congo red paper (Note 11). The oily suspension is extracted with two 200-ml. portions of ether in a 2-l. separatory funnel. The ether extracts are washed with two 100-ml. portions of water and dried over 45 g. of anhydrous sodium sulfate. The dried ether extract is transferred to a 1-l. Erlenmeyer flask and concentrated on a steam bath until ether is no longer distilled. To the residue there is added 500 ml. of warm (50–60°) concentrated hydrochloric acid (in a hood), and the suspension is allowed to cool with occasional swirling (Note 12). Crystallization is completed by chilling in ice, and the product is collected on a sintered-glass funnel. After the product has been dried as much as possible on the funnel it is dried to constant weight in a vacuum desiccator over solid potassium hydroxide. The yield of dry acid is 82–84 g. (80–82%), m.p. 77.5–79.5°. It is satisfactory for most purposes. If very pure material is desired the acid may be recrystallized from three volumes of hexane to give material, m.p. 78.5–79.5°, in 90–95% recovery.

2. Notes

1. The hydrogen chloride may be generated by the method described in *Organic Syntheses*, Coll. Vol. **1**, 293 (1941). It should be dried by passage through concentrated sulfuric acid. The hydrogen chloride may be taken directly from a cylinder, if one is available.

2. The flask should be rinsed with a small portion of water.

3. The amount of bicarbonate solution varies, depending on the weight of hydrogen chloride used. There is usually required 250–350 ml.

4. The submitters used Matheson thionyl chloride without further purification.

5. The flask should be rinsed with a small portion of ether.

6. The solution becomes homogeneous after a few minutes of heating.

7. The checkers found that about 250–270 ml. of distillate is obtained under these conditions.

8. About 90–130 g. of sodium bicarbonate is usually required.

9. When the combined ether layers are dried over sodium sulfate and concentrated, and the residue is distilled at reduced pressure, about 11 g. (10%) of unchanged ethyl α-chlorophenylacetate, b.p. 134–137°/15 mm., is recovered.

10. The solution should be kept ice-cold during the extraction, which must be carried out rapidly lest hydrolysis of the chlorophenylacetic acid to mandelic acid take place.

11. About 70 ml. of acid is required. A 25-ml. excess of 12 *N* sulfuric acid is recommended in order to insure the acidity of the mixture.

12. The objective of the hydrochloric acid treatment is to remove small amounts of mandelic acid from the product. If

seed crystals are available, the slurry should be seeded as it is cooled.

3. Methods of Preparation

α-Chlorophenylacetic acid has been prepared from mandelonitrile and hydrochloric acid in a sealed tube,[2,3] from mandelic acid and hydrochloric acid in a sealed tube,[4] from α-nitrostyrene and hydrochloric acid in a sealed tube,[5] from phenylglycine, hydrochloric acid, and sodium nitrite,[6] from mandelic acid and phosphorus pentachloride (to give the acid chloride which is then hydrolyzed),[7] and, in poor yield, from mandelic acid and thionyl chloride.[8] In the method described, ethyl mandelate is prepared according to Fischer and Speier.[9] The conversion to the chloroester and the acid hydrolysis step are modifications of a preparation described by McKenzie and Barrow.[8]

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[1] Department of Chemistry, University of Notre Dame, Notre Dame, Indiana.
[2] Spiegel, *Ber.*, **14**, 239 (1881).
[3] Meyer, *Ann.*, **220**, 41 (1883).
[4] Radziszewski, *Ber.*, **2**, 208 (1869).
[5] Priebs, *Ann.*, **225**, 336 (1884).
[6] Jochem, *Z. physiol. Chem.*, **31**, 123 (1900).
[7] Bischoff and Walden, *Ann.*, **279**, 122 (1894).
[8] McKenzie and Barrow, *J. Chem. Soc.*, **99**, 1916 (1911).
[9] Fischer and Speier, *Ber.*, **28**, 3252 (1895).

N-2-CYANOETHYLANILINE

(Propionitrile, β-anilino-)

$$C_6H_5NH_2\cdot HCl + (C_2H_5)_2NH + CH_2{=}CHCN \rightarrow C_6H_5NHCH_2CH_2CN + (C_2H_5)_2NH\cdot HCl$$

Submitted by J. Cymerman-Craig and M. Moyle.[1]
Checked by William S. Johnson and Duff S. Allen, Jr.

1. Procedure

A mixture of 12.95 g. (0.10 mole) of aniline hydrochloride (Note 1), 6.6 g. (0.12 mole) of acrylonitrile, and 9.1 g. (0.12

mole) of diethylamine (Note 2) is placed in a 100-ml. round-bottomed flask fitted with an efficient reflux condenser and heated for 2.5 hours in a bath maintained at 180°.

The melt is cooled to 0°, 50 ml. of 10% aqueous sodium hydroxide solution is added, and the mixture is extracted with four 50-ml. portions of chloroform. The combined chloroform extracts are washed with two 25-ml. portions of water, and these in turn are extracted with 10 ml. of chloroform. The organic layers are combined and dried partially over anhydrous sodium sulfate. The solvent is removed by distillation on the steam bath, and the residue is distilled at reduced pressure from a 50-ml. distilling flask. After a fore-run of about 4 g. (Note 3), b.p. 60–70°/1.5 mm. (bath temperature taken up to 125°), the cyanoethylaniline is collected at 115–120°/0.01 mm. The product solidifies in the form of colorless plates, m.p. 48–51° (Note 4). The yield is 10.5–11.4 g. (72–78%) (Note 5).

2. Notes

1. An equimolar quantity of aniline benzenesulfonate may be used in place of the hydrochloride.
2. No reaction occurs if the diethylamine is omitted.
3. In a typical run this fraction weighed 4.4 g. and contained 1.6 g. of aniline (estimated as acetanilide) and 2.8 g. of 3-diethylaminopropionitrile.
4. Reported properties are b.p. 178–186°/16 mm. and m.p. 51.5°.[2]
5. The submitters have found that other arylamines may be employed in a similar manner in place of aniline. Thus N-2-cyanoethyl-*p*-anisidine was obtained in 76% yield as plates, m.p. 62–64°, b.p. 130–140°/0.01 mm.; N-2-cyanoethyl-*m*-chloroaniline, in 42% yield as needles, m.p. 44–46°, b.p. 125–130°/0.01 mm.; N,N′-bis-2-cyanoethyl-*o*-phenylenediamine, in 70% yield as needles, m.p. 116–118°, b.p. 190–200°/0.01 mm.; and N,N′-bis-2-cyanoethyl-*p*-phenylenediamine in 22% yield as plates, m.p. 138–139°.

3. Methods of Preparation

N-2-cyanoethylaniline has been prepared (accompanied by much of the N,N′-bis-2-cyanoethyl compound) by heating aniline, acrylonitrile and acetic acid either in an autoclave,[2,3] or at refluxing temperature for 10 hours in the presence of various inorganic catalysts.[4] The substance has also been obtained, free of the N,N′-bis-2-cyanoethyl compound, from aniline salts and β-diethylaminopropionitrile.[5,6,7]

[1] The University of Sydney, Sydney, Australia.

[2] Cookson and Mann, *J. Chem. Soc.*, **1949**, 67.

[3] Braunholtz and Mann, *J. Chem. Soc.*, **1952**, 3046.

[4] Braunholtz and Mann, *J. Chem. Soc.*, **1953**, 1817.

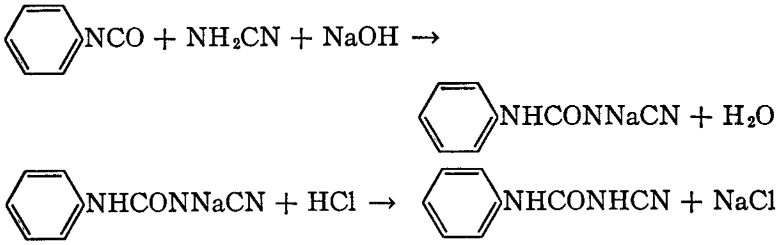
[5] Bauer and Cymerman, *Chemistry & Industry*, **1951**, 615.

[6] Bauer, Cymerman, and Sheldon, *J. Chem. Soc.*, **1951**, 3311.

[7] Bekhli, *Zhur. Obshcheĭ Khim.*, **21**, 86 (1951) [*C. A.*, **45**, 7540 (1951)].

1-CYANO-3-PHENYLUREA

(Urea, 1-cyano-3-phenyl-)



Submitted by Frederick Kurzer and J. Roy Powell.[1]
Checked by John C. Sheehan and Ernest R. Gilmont.

1. Procedure

To a solution of 16.8 g. (0.40 mole) of cyanamide in 50 ml. of water (Note 1) contained in a 400-ml. flask or beaker is added 50 ml. of aqueous 3 *N* sodium hydroxide (0.15 mole). To the resulting solution, cooled to 15–18°, is added, in 2-ml. portions with shaking over a 15–18 minute period, 23.8 g. (22.0 ml., 0.2 mole) of phenyl isocyanate. The isocyanate dissolves rapidly, while the temperature rises slightly. The mixture is maintained at 20–25° by occasional external cooling in ice water. When half the phenyl isocyanate has been introduced, a second portion of 50 ml. (0.15 mole) of 3 *N* sodium hydroxide is added to keep the reaction mixture strongly alkaline throughout the experiment. When addition is complete (Note 2), the slightly turbid liquid is diluted with 40 ml. of water and is filtered immediately under reduced pressure (Note 3) to remove undissolved impurities and traces of separated diphenylurea (Note 4). The cyanourea is precipitated from the clear colorless filtrate by the slow addition of concentrated hydrochloric acid with stirring until a permanent turbidity just appears (Note 3). Cracked ice (30–40 g.) is added to lower the temperature to 18–20°. Precipitation is then completed in this temperature range by the alternate addition of concentrated hydrochloric acid (total volume required, approximately 30 ml.) and cracked ice until the suspension is acid to Congo red. The crude cyanourea forms a microcrystalline, white precipitate, which, after storage at 0° for 3 hours, is collected by filtration under reduced pressure (Note 5) and is washed with two portions of cold water (20–25 ml.) (Note 6). The crude product is drained thoroughly, air-dried at room temperature, and finally dried to constant weight in a desiccator over phosphorus pentoxide. The yield of crude 1-cyano-3-phenylurea (Note 7), m.p. 122–126° with decomposition (Note 8), varies between 29 and 30.5 g. (90–95%). The dried material is purified as follows. A solution of the crude product in 100 ml. of boiling acetone is diluted slowly with gentle swirling with 30–40 ml. of petroleum ether (boiling range 40–60°). As crystallization proceeds, an additional 20–30 ml. of petroleum ether is added carefully at such a rate that the supernatant liquid does not become turbid. After 15 minutes at room temperature, the mixture is set aside at 0°. The product is collected by filtration under reduced pressure and washed successively with 50 ml. of an acetone-petroleum ether mixture (1:3) and 50 ml. of petroleum ether. 1-Cyano-3-phenylurea thus obtained forms colorless lustrous needles, m.p. 127–128° with decomposition (Note 8), yield 20–21.5 g. (62–67%). Slow dilution of the filtrates with petroleum ether to a total volume of 350–400 ml. and storage at 0° affords a second crop, m.p. 123–126° (dec.), of satisfactory purity; yield 4–5 g. (12–16%). The synthesis is generally applicable to the preparation of 1-cyano-3-arylureas (Note 9).

2. Notes

1. The checkers used 16.8 g. of Eastman Kodak Company cyanamide (P1995) without further purification. A convenient method of preparing cyanamide from commercial calcium cyanamide has been described.[2] According to the submitters, an aqueous solution of crude cyanamide is satisfactory in the present synthesis and is obtained by adapting this published procedure [2] as follows.

The residual crude cyanamide remaining after evaporation of the ethereal extracts (which need not be dried previously) is dissolved readily in the appropriate volume of cold water. A small quantity of water-insoluble oily or semisolid by-products is removed by shaking the solution with carbon and filtering the liquid through a small ordinary filter, followed by rinsing with a few milliliters of water. The clear filtrate is suitable for the subsequent operation.

In order to allow for small losses in the filtration and for the presence of impurities (such as solvent and oily by-products) an excess of approximately 10–15% by weight of crude cyanamide is allowed.

2. The reaction is completed when the liquid no longer has the odor of phenyl isocyanate; shaking is continued until this stage is reached.

3. The reaction mixture is not cooled during the addition of the last two or three portions of phenyl isocyanate, so that the final temperature is near 25°; this procedure prevents separation of the sodium salt of cyanophenylurea, which crystallizes readily at low temperatures. For the same reason, the filtered solution of the salt is not precooled, but rather is cooled during the precipitation of the free cyanourea.

4. The residue on the filter is rinsed with 5–10 ml. of water, in order to redissolve any small quantities of the sodium salt of cyanophenylurea that may have been collected.

5. The aqueous filtrate does not deposit any further material on storage at 0° and is discarded.

6. For the purpose of washing, the filter cake on the funnel is covered with ice water. After being allowed to remain in contact for a few seconds, the liquid is quickly drained under reduced pressure. The second portion of washing water should no longer be acid to Congo red.

7. According to the submitters the crude material may turn very pale pink on drying, but the product is again colorless after recrystallization. The checkers found that the crude product could be dried to less than 0.2% moisture by drawing air through the filter cake for 3 hours.

8. The decomposition temperature is somewhat influenced by the rate of heating. The material does not form a clear melt during the decomposition.

9. According to the submitters 1-cyano-3-α-naphthylurea [6] is obtained similarly from α-naphthyl isocyanate in 85–90% yields. Crystallization from acetone-petroleum ether (12 and 6 ml., respectively, per gram of crude product; recovery approximately 60% per crystallization) yields lustrous prisms, m.p. 148–149° with decomposition.

3. Methods of Preparation

1-Cyano-3-phenylurea, first obtained by the alkaline hydrolysis of 5-anilino-3-*p*-toluyl-1,2,4-oxadiazole,[3] has been prepared by the condensation of phenyl isocyanate and the sodium salt of cyanamide.[4] However, in these publications an incorrect structural assignment for the product was made. 1-Cyano-3-phenylurea is obtained also, together with other products, by warming gently 1-cyano-3-phenylthiourea with caustic soda in the presence of ethylene chlorohydrin,[5] or by gradually adding caustic potash to a boiling solution of 1-phenyldithiobiuret and ethylene chlorohydrin in ethanol.[5]

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

[2] Kurzer and Lawson, *Org. Syntheses*, **34**, 67 (1954).

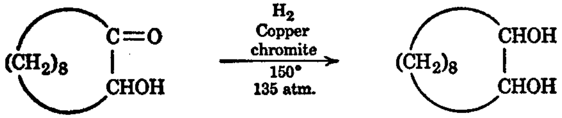
[3] Böeseken, *Rec. trav. chim.*, **16**, 350 (1897).

[4] Böeseken, *Rec. trav. chim.*, **29**, 279 (1910).

[5] Fromm and Wenzl, *Ber.*, **55B**, 809 (1922).

[6] Kurzer and Powell, *J. Chem. Soc.*, **1955**, 1500.

1,2-CYCLODECANEDIOL



(*cis* and *trans*)

Submitted by A. T. Blomquist and Albert Goldstein.[1]
Checked by N. J. Leonard and F. H. Owens.

1. Procedure

A mixture of 140 g. (0.82 mole) of sebacoin[2] (Note 1), 50 g. of copper chromite catalyst[3] (Note 2), and 230 ml. of 95% ethanol is placed in an 800-ml. high-pressure hydrogenation bomb (Note 3). Hydrogen is admitted to the bomb at 135 atm., and the bomb is heated to 150°. When this temperature is reached, the shaker is started. The temperature is stabilized at 150° after its initial rapid fluctuation, and the hydrogenation is allowed to proceed until the mixture ceases to absorb hydrogen (2–4 hours). The heating and shaking are discontinued, and the bomb is allowed to cool to room temperature. The excess hydrogen is vented, and the bomb is dismantled.

The *cis*-1,2-cyclodecanediol will have crystallized out of solution, while the *trans*-diol remains in the ethanol. The entire mixture is washed out of the bomb with 95% ethanol (about 1 l.). The *cis*-glycol is redissolved by heating the ethanolic mixture at reflux temperature. Filter aid ("Celite") is added to the mixture, and the hot mixture is filtered through a bed of filter aid on a Büchner funnel to remove the catalyst. The ethanol is removed from the filtrate by distillation on a steam bath under water-pump pressure. The residue is dissolved in a minimum of hot 1:1 benzene-ethanol solution (about 250 ml.), and the *cis*-diol crystallizes upon cooling to room temperature. The crystals are collected by filtration, and the mother liquor is concentrated to dryness on a steam bath under water-pump pressure. The residue is again dissolved in a minimum of hot 1:1 benzene-ethanol (about 100 ml.), and additional *cis*-diol crystallizes upon cooling in a refrigerator. The process is repeated using 50 ml. of 1:1 benzene-ethanol solvent. The total yield of *cis*-1,2-cyclodecanediol is 68–73 g. (48–52%), m.p. 137–138°.

The *trans*-diol remains in the mother liquor and may be recovered by complete evaporation of the solvent followed by recrystallization of the residue from pentane. The yield of *trans*-1,2-cyclodecanediol is 38–45 g. (27–32%), m.p. 53–54°.

2. Notes

1. A sebacoin-sebacil mixture may be used.
2. A commercial catalyst was employed by the submitters: Harshaw Chemical Company, CU-0202P; 556-002.
3. A suitable apparatus is the "Aminco" high-pressure hydrogenation apparatus, manufactured by the American Instrument Company, Silver Springs, Maryland.

3. Methods of Preparation

1,2-Cyclodecanediol has been prepared by the hydrogenation of sebacoin in the presence of Raney nickel[4] or platinum,[5] by the reduction of sebacoin with aluminum isopropoxide[5] or lithium aluminum hydride,[5] and by the oxidation of cyclodecene with osmium tetroxide and pyridine.[4]

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[1] Cornell University, Ithaca, New York.

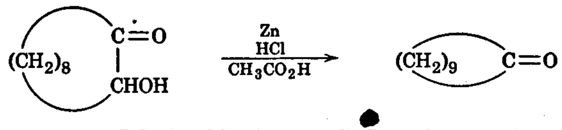
[2] Allinger, *Org. Syntheses*, **36**, 79 (1956).

[3] Lazier and Arnold, *Org. Syntheses*, Coll. Vol. **2**, 142 (1943), Note 11.

[4] Prelog, Schenker, and Günthard, *Helv. Chim. Acta*, **35**, 1598 (1952).

[5] Blomquist, Burge, and Sucsy, *J. Am. Chem. Soc.*, **74**, 3636 (1952).

CYCLODECANONE



Submitted by Arthur C. Cope, John W. Barthel, and
Ronald Dean Smith.[1]
Checked by N. J. Leonard and J. C. Little.

1. Procedure

A 1-l. round-bottomed three-necked flask is fitted with a sealed stirrer (Note 1), a dropping funnel, and a reflux condenser, through which a thermometer extends nearly to the bottom of the flask. In the flask are thoroughly mixed 40.5 g. (0.62 gram atom) of zinc dust (Note 2) and 100 ml. of glacial acetic acid, and to this mixture is added 42.5 g. (0.25 mole) of sebacoin[2] (Note 3). The mixture is stirred rapidly, and 90 ml. of concentrated c.p. hydrochloric acid is added dropwise during a period of 5 to 10 minutes, or as fast as control of foaming and temperature permits. The temperature must be kept between 75 and 80° (Note 4), and cooling by a water bath may be necessary during the addition of the hydrochloric acid. Stirring is continued for 1.5 hours at 75–80°. Thirty minutes after the initial addition of hydrochloric acid, and again 30 minutes later, 90-ml. portions of concentrated hydrochloric acid are added to the mixture while the temperature is maintained at 75–80°. After the reaction is complete, the remaining zinc is separated from the cooled mixture by decantation (Note 5). The liquid phase is diluted with 700 ml. of saturated aqueous sodium chloride solution and extracted with four 250-ml. portions of ether, each of which is first used to wash the residual zinc (Note 6). The ether extracts are combined and washed with 250 ml. of saturated sodium chloride solution, three 250-ml. portions of 10% sodium carbonate solution (Foaming!), and finally 250 ml. of saturated sodium chloride solution. The ethereal solution is dried over anhydrous magnesium sulfate (about 25 g. is needed). After the drying agent has been removed by filtration and the solvent by distillation, the residue is distilled at reduced pressure through an efficient column (Note 7). After a small fore-run consisting mostly of cyclodecane, cyclodecanone is collected at 99–101°/8 mm. The yield is 29–30 g. (75–78%), n_D^{25} 1.4808–1.4810 (Note 8).

2. Notes

1. A metal stirrer must not be used. A simple glass stirrer with a ball-joint seal is satisfactory.
2. Mallinckrodt technical grade may be used.[3] If Mallinckrodt analytical reagent zinc dust is used, the reaction temperature must be maintained at 50–55° instead of 75–80°.
3. Pure sebacoin gives a colorless product. A sebacoin-sebacil mixture must first be purified by recrystallization from pentane as described.[2] The sebacil apparently is not reduced completely according to the accompanying directions and thus may contaminate the product (see Note 7).
4. The reaction temperature is important. At temperatures below 75° some sebacoin remains unreduced, while at temperatures above 80° considerable cyclodecane is formed. The submitters report that the reaction run at the reflux temperature gives cyclodecanone in 27% yield and cyclodecane in 32% yield.
5. The product should be isolated and distilled as quickly as possible inasmuch as the unreacted sebacoin is readily oxidized to sebacil, which cannot be separated from the cyclodecanone by simple distillation.
6. The residual zinc may be pyrophoric.
7. For efficient separation of cyclodecanone from cyclodecane, a 60-cm. column of the simple Podbielniak type[4] may be used. Removal of sebacil cannot be accomplished readily by fractional distillation, since cyclodecanone and sebacil have virtually identical boiling points.
8. Cyclodecanone regenerated from its semicarbazone, m.p. 203.5–205.5°, has n_D^{25} 1.4806.

3. Methods of Preparation

The procedure described is a modification of the directions of Prelog, Frenkiel, Kobelt, and Barman.[5] Cyclodecanone has been prepared by the dehydration of sebacoin followed by catalytic hydrogenation,[6] by the pyrolysis of the thorium or yttrium salt of nonane-1,9-dicarboxylic acid,[7] and by the ring enlargement of cyclononanone,[8] as well as by the reduction of sebacoin.[9]

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[1] Massachusetts Institute of Technology, Cambridge 39, Massachusetts.

[2] Allinger, *Org. Syntheses*, **36**, 79 (1956).

[3] Brown and Borkowski, *J. Am. Chem. Soc.*, **74**, 1901 (1952).

[4] Cason and Rapoport, *Laboratory Text in Organic Chemistry*, p. 238, Prentice-Hall, New York, 1950.

[5] Prelog, Frenkiel, Kobelt, and Barman, *Helv. Chim. Acta*, **30**, 1741 (1947).

[6] Stoll, *Helv. Chim. Acta*, **30**, 1837 (1947).

[7] Ruzicka, Stoll, and Schinz, *Helv. Chim. Acta*, **9**, 249 (1926); **11**, 670 (1928).

[8] Kohler, Tishler, Potter, and Thompson, *J. Am. Chem. Soc.*, **61**, 1057 (1939).

[9] Blomquist, Burge, and Sucsy, *J. Am. Chem. Soc.*, **74**, 3636 (1952).

DIAZOMETHANE

(Methane, diazo-)

$$p\text{-}CH_3C_6H_4SO_2N(NO)CH_3 + ROH \xrightarrow{KOH} CH_2N_2 + p\text{-}CH_3C_6H_4SO_2OR + H_2O$$

Submitted by TH. J. DEBOER and H. J. BACKER.[1]
Checked by JAMES CASON, MAX J. KALM, and R. F. PORTER.

1. Procedure

Caution! Diazomethane is toxic and prone to cause development of specific sensitivity. A well-ventilated hood should be used for the entire procedure.

A 125-ml. distilling flask is fitted (Note 1) with a condenser set for distillation and with a long-stem dropping funnel. The condenser is connected by means of an adapter to a 250-ml. Erlenmeyer flask. Through a second hole in the stopper of the

Erlenmeyer flask is placed an outlet tube bent so as to pass into and nearly to the bottom of a second Erlenmeyer flask which is not stoppered. Both receivers are cooled in an ice-salt mixture; in the first is placed 10 ml. of ether (Note 2), and in the second 35 ml. of ether. The inlet tube passes below the surface of the ether in the second flask.

In the distilling flask are placed a solution of 6 g. of potassium hydroxide dissolved in 10 ml. of water, 35 ml. of Carbitol (Note 3), 10 ml. of ether (Note 2), and the "Teflon"-coated bar of a magnetic stirrer (Note 4). The dropping funnel is attached and adjusted so that the stem is just above the surface of the solution in the distilling flask. There is placed in the dropping funnel a solution of 21.5 g. (0.1 mole) of *p*-tolylsulfonylmethylnitrosamide [2] in 125 ml. of ether (Note 5). The distilling flask is heated in a water bath (Note 4) at 70–75°, the stirrer is started, and the nitrosamide solution is added at a regular rate during 15–20 minutes. As soon as all the nitrosamide solution has been added, additional ether (Note 2) is placed in the dropping funnel and added at the previous rate until the distillate is colorless. Usually, 50–100 ml. additional of ether is required. The distillate contains 2.7–2.9 g. (64–69%) of diazomethane, as determined by titration [3] (Note 6).

2. Notes

1. The checkers have been advised by Professor Fritz Arndt, in a private communication, that he has never encountered an explosion in handling diazomethane. He attributes the explosions frequently reported to the presence in the system of sharp or rough surfaces, especially ground joints. It is recommended that all glass tubes be carefully fire-polished and that connections be made with carefully fitted corks or rubber stoppers. Etched or scratched flasks should not be used. The submitters report that they have encountered no explosions during this method of preparation of diazomethane, and the checkers have used the method on numerous occasions during a period of about two years without encountering an explosion. Nevertheless, diazomethane has a bad reputation, and it is recommended that the

operator wear gloves and goggles, and work behind a safety screen or a hood door with safety glass.

2. If an alcohol-free solution of diazomethane is required, absolute ether should be used throughout this preparation.

3. The Carbitol (monoethyl ether of diethylene glycol) was the Carbide and Carbon Chemicals Company product, which was distilled before use, b.p. 192–196°. It is a suitable solvent to render the reactants mutually soluble. Aqueous alkali with an ether solution of the nitrosamide does not yield diazomethane.

4. The same results may be obtained by an occasional careful agitation of the flask by hand; however, an explosion during this agitation by hand would be unfortunate. If the flask is placed in contact with the bottom of a beaker containing the heated water, and the magnetic stirring unit is placed in contact with the beaker, the bar may be spun satisfactorily. The checkers used the magnetic stirring apparatus, no. 9235-R, supplied by the A. H. Thomas Company, Philadelphia, Pa., and heated the water bath with the thermostated electric immersion heater, "Chill Chaser," model S-1005, supplied by the Still-Man Company, New York 56, N. Y. Satisfactory results should also be obtained by use of a combined heater and magnetic stirrer, such as no. 25210T supplied by the Will Corporation, New York 12, N. Y.

5. Nitrosamide prepared as previously described,[2] not recrystallized, is suitable for the present preparation. The solubility of the nitrosamide in ether drops sharply with temperature; below 20°, more than the specified amount of ether may be required, especially if recrystallized nitrosamide is used.

6. If an entirely dry solution of diazomethane is required, round pellets of potassium hydroxide should be used.[3]

3. Methods of Preparation

The more important methods of preparation of diazomethane include those from nitrosomethylurea,[3] nitrosomethylurethane,[4] N-nitroso-β-methylaminoisobutyl methyl ketone,[5] and 1-methyl-1-nitroso-3-nitroguanidine.[6, 7]

The advantage of the present method[8] resides in the stability of the starting material[2] and the manipulative advantage resulting from its solubility in organic solvents.

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[1] Organisch Chemisch Laboratorium der Rijks-Universiteit, Groningen, The Netherlands.

[2] de Boer and Backer, *Org. Syntheses*, **34**, 96 (1954).

[3] Arndt, *Org. Syntheses*, Coll. Vol. **2**, 165 (1943).

[4] McPhee and Klingsberg, *Org. Syntheses*, Coll. Vol. **3**, 119 (1955).

[5] Redemann, Rice, Roberts, and Ward, *Org. Syntheses*, Coll. Vol. **3**, 244 (1955).

[6] McKay, *J. Am. Chem. Soc.*, **70**, 1974 (1948); **71**, 1968 (1949).

[7] McKay, Ott, Taylor, Buchanan, and Crooker, *Can. J. Research*, **28B**, 683 (1950).

[8] de Boer and Backer, *Rec. trav. chim.*, **73**, 229 (1954).

1,1-DICHLORO-2,2-DIFLUOROETHYLENE

(Ethylene, 1,1-dichloro-2,2-difluoro-)

$$CCl_3{-}CClF_2 + Zn \xrightarrow{CH_3OH} CCl_2{=}CF_2 + ZnCl_2$$

Submitted by J. C. SAUER.[1]
Checked by CHARLES C. PRICE and MASEH OSGAN.

1. Procedure

In a 500-ml. three-necked round-bottomed flask equipped with a 100-ml. separatory funnel, a thermometer, and a short fractionating column (Note 1) leading through a condenser to a 100-ml. tared receiver are charged 150 ml. of methanol, 42.2 g. (0.65 gram atom) of powdered zinc, and 0.2 g. of zinc chloride. Acetone cooled in a Dry Ice-acetone bath is circulated through the condenser, and the distillation receiver is immersed in ice water (Note 2). The mixture in the flask is heated to 60–63°, and a 10–15-ml. portion of a solution consisting of 122.4 g. (0.6 mole) of 1,1,1,2-tetrachloro-2,2-difluoroethane (Note 3) in 50 ml. of methanol is added dropwise over a period of a few minutes. The reaction generally becomes moderately vigorous at this point, and refluxing of 1,1-dichloro-2,2-difluoroethylene part-way up the column is observed. The heating bath is removed at this time. Addition of the ethane derivative is continued at such a rate that the temperature of the refluxing liquid at the head of the column is maintained at 18–22°. The flask may require occasional shaking to prevent the zinc dust from agglomerating. The take-off rate of the ethylene derivative is adjusted to about one-half the rate of input of the ethane derivative. During this addition, the temperature in the distillation flask drops to 45–50°. The addition of the ethane derivative requires 45 minutes to 1 hour. The heating bath is replaced, and another hour is required to complete the dehalogenation and to distil the last of the product. The temperature in the distillation flask during this period gradually rises to 69–70°. There is collected in the receiver 71–76 g. (89–95% yield) (Note 4) of 1,1-dichloro-2,2-difluoroethylene, distilling at 18–21° (Note 5), n_{D}^{0}, 1.3730–1.3746.

2. Notes

1. A 16-in. column packed with platinum gauze and fitted with a variable take-off was used by the submitters. The checkers used a 20 × $\frac{3}{4}$-in. jacketed column packed with $\frac{1}{16}$-in. glass helices.
2. The checkers used a Dry Ice-acetone-cooled cold-finger condenser fitted with a partial take-off adapter.
3. Tetrachlorodifluoroethane ($CCl_3—CClF_2$) is sold under the trade name "Genetron-131" by the General Chemical Division, Allied Chemical and Dye Corporation, 40 Rector Street, New York 6, N. Y. The sample, as received, melted at 38–40°. According to infrared data, the compound was 95–99% pure. Distillation through a high-precision, spinning band column showed about 10% distilling at 86–90° (mostly 90°), another 10% at 90–90.5°, and the balance at 91°. All fractions were essentially the same by infrared analysis. The first fraction melted at about 35°, and the main fraction melted at 40.5°.[2]
4. This product contains 1–1.7% methanol and a trace of the starting material.
5. This figure is slightly above the true boiling point of 1,1-dichloro-2,2-difluoroethylene. Upon redistillation in a low-temperature still fitted with a thermocouple, about 95% of this material distilled at 17°,[3] n_{D}^{3} 1.3710.

3. Methods of Preparation

1,1-Dichloro-2,2-difluoroethylene has been prepared by the zinc dehalogenation method in ethanol.[2,3] This compound has also been prepared by dehydrochlorination of 1,2,2-trichloro-1,1-difluoroethane by a solution of potassium hydroxide in aqueous methanol[4] or by thermal cleavage at 590°.[5]

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[1] Contribution No. 285 from the Chemical Department, Experimental Station, E. I. duPont de Nemours and Company, Wilmington, Delaware.

[2] Locke, Brode, and Henne, *J. Am. Chem. Soc.*, **56**, 1726 (1934).

[3] Henne and Wiest, *J. Am. Chem. Soc.*, **62**, 2051 (1940).

[4] McBee, Hill, and Bachman, *Ind. Eng. Chem.*, **41**, 70 (1949).

[5] Padbury and Tarrant (to American Cyanamid Company), U. S. pat. 2,566,807 [*C. A.*, **46**, 2561 (1952)].

N,N'-DIETHYLBENZIDINE

(Benzidine, N,N'-diethyl-)

$$H_2NC_6H_4C_6H_4NH_2 + 2C_2H_5OH \xrightarrow[\text{Ni}]{\text{Raney}} C_2H_5NHC_6H_4C_6H_4NHC_2H_5 + 2H_2O$$

Submitted by Rip G. Rice and Earl J. Kohn.[1]
Checked by Max Tishler, W. H. Jones, and W. F. Benning.

1. Procedure

In a 5-l. three-necked flask, fitted with an efficient stirrer (Note 1), a stopper, and a reflux condenser, are placed, in order, 184.2 g. (1 mole) of benzidine (Note 2), 500 ml. of commercial absolute ethanol, about 125 g. of Raney nickel,[2] and 500 ml. of ethanol. The mixture is heated under reflux with stirring for a total of 15 hours (Note 3). The volume is brought to 3 l. with 95% ethanol, and about 150 g. of filter aid ("Super-Cel") is added with stirring. The mixture is heated to boiling, filtered rapidly through a ¼-in. layer of filter aid on a Büchner funnel into a 4-l. filter flask (Notes 4 and 5), and the nickel is washed well with hot 95% ethanol (Note 6). The filtrate is concentrated to a volume of 1.5 l., cooled slowly to room temperature, then chilled in a refrigerator and filtered. The yield is 185–202 g. (77–84%) of light gray or purplish gray flakes, m.p. 105–115°.

The crude product is dissolved in 1.5 l. of hot 95% ethanol, the solution is treated with 5 g. of activated carbon, and the mixture is filtered rapidly with suction. The filtrate is made up to 1.5 l. with 95% ethanol and heated to dissolve the solid. The solution is allowed to cool slowly to room temperature, then chilled in a refrigerator and filtered. The yield is 143–161 g. (60–67%) of colorless flakes melting at 115–116° (Note 7).

2. Notes

1. Efficient stirring is necessary to keep the nickel uniformly distributed throughout the reaction mixture. Otherwise the yield is decreased considerably.

2. The submitters used benzidine obtained by neutralization of an aqueous solution of C.P. benzidine dihydrochloride (Matheson, Coleman and Bell) with 20% sodium hydroxide solution, followed by crystallization from 60–70% ethanol. The benzidine prepared in this manner was in the form of light tan flakes. Freshly prepared benzidine should be used for the best results.

3. The refluxing time does not have to be continuous. The submitters heated the reaction mixture 7 hours, allowed the mixture to stand overnight, and continued the refluxing the next day.

4. This operation should be carried out in a well-ventilated hood.

5. To prevent clogging of the Büchner funnel during filtration it is necessary to preheat the funnel and keep it hot during filtration.

6. The nickel is pyrophoric and must be kept moist to prevent spontaneous ignition.

7. The method has been applied successfully by the submitters[3] to the preparation of N,N′-dibutylbenzidine (61% crude yield), N-ethyl-, N-propyl-, N-butyl-, N-amyl-, and N-benzylanilines (80–84% yields), N-hexylaniline (72%), and N-isobutyl- and N-isoamylanilines (41, 49%). N-Propylbutylamine was obtained from propyl alcohol and butylamine in 57% yield. The submitters state that no alkylation of benzidine took place with methyl alcohol or of aniline with methyl, isopropyl, or *sec*-butyl alcohol. The method has been applied to the synthesis of other N-alkyl and N-cycloalkyl aromatic amines.[4,5]

3. Methods of Preparation

N,N′-Diethylbenzidine has been prepared by heating ethyl iodide, benzidine, and ethanol in a pressure tube at water-bath temperature,[6,7] and by the reaction of diethylzinc on benzenediazonium chloride.[7] The method described here is a modification of that of Shah, Tilak, and Venkataraman.[8]

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[1] Naval Research Laboratory, Washington, D. C.

[2] Mozingo, *Org. Syntheses*, Coll. Vol. **3**, 181 (1955).

[3] Rice and Kohn, *J. Am. Chem. Soc.*, **77**, 4052 (1955).

[4] Ainsworth, *J. Am. Chem. Soc.*, **78**, 1636 (1956).

[5] Kao, Tilak, and Venkataraman, *J. Sci. Ind. Research India*, **14B**, 624 (1955).

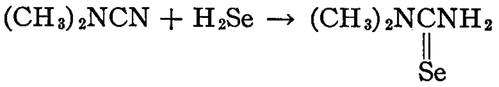
[6] Hofmann, *Ann.*, **115**, 365 (1860).

[7] Bamberger and Tichvinsky, *Ber.*, **35**, 4179 (1902).

[8] Shah, Tilak, and Venkataraman, *Proc. Indian Acad. Sci.*, **28A**, 145 (1948).

N,N-DIMETHYLSELENOUREA

(Urea, 1,1-dimethyl-2-seleno-)



$$(CH_3)_2NCN + H_2Se \rightarrow (CH_3)_2N\underset{\underset{Se}{\|}}{C}NH_2$$

Submitted by FRANK BENNETT and RALPH ZINGARO.[1]
Checked by C. F. H. ALLEN and K. C. KENNARD.

1. Procedure

Caution! Hydrogen selenide is very toxic. This preparation should be carried out in a well-ventilated hood. The operator should wear rubber gloves. The apparatus should be screened from any bright light.

A mixture of 37 g. (0.5 mole) of dimethylcyanamide (Note 1), 75 ml. of concentrated ammonium hydroxide, and 25 ml. of water is placed in a 250-ml. round-bottomed three-necked flask fitted with a stirrer, thermometer, and glass delivery tube (Note 2). The solution is stirred slowly, while hydrogen selenide (Note 3) is slowly bubbled in, maintaining the temperature at 20–30° by occasional external cooling. At the end of the reaction (4–5 hours) when there is no more gas evolution from the generator (4–5 hours), the flask and contents are cooled to 5–10° and stirred vigorously for one-half hour. The solid is then collected on a 9-cm. Büchner funnel and washed with 250 ml. of ice-cold 95% ethanol. The crude, gray product weighs 65–73 g. (86–97%).

For purification, it is dissolved in 9–9.5 l. of boiling benzene (Note 4). The solution is filtered rapidly, using a 32-cm. folded filter in an 8-in. short-stem glass funnel. The recovery is 59–70 g. The fine, white crystals, which melt at 169–170° (Note 5), are stored in a brown glass bottle under nitrogen (Notes 6, 7, 8).

2. Notes

1. The practical grade, b.p. 162–164°, obtained from the Eastman Kodak Company, was used.

2. A tube 8 mm. in diameter is used. A sintered-glass gas addition tube is quickly clogged by selenium.

3. Hydrogen selenide is generated from iron or aluminum selenide and a mineral acid. Into a 2-l. three-necked flask, fitted with sealed stirrer, reflux condenser, and dropping funnel are placed 135 g. (1 mole) of powdered iron selenide (Note 9) and 350 ml. of water. The generator is heated on a steam cone, while 350 ml. of concentrated hydrochloric acid is admitted slowly with stirring, so that the hydrogen selenide is evolved at a steady rate. (The generation of gas is regulated both by the rate of heating and the rate of addition of acid, so that the gas is absorbed almost entirely; it is led from the top of the condenser to the delivery tube.) The amount of selenide used is sufficient. The residual liquid in the generator is left open to the air overnight in a hood. Then sufficient 50% sodium hydroxide solution is added to make it basic, and the whole is flushed down the sink, using a large amount of water.

4. Recrystallization from benzene affords a product that has superior storage qualities. A liter dissolves 5–6 g. at the boiling point.

5. The melting point is unchanged by further recrystallization.

6. The product turns pink, and eventually gray, if exposed to air for an extended period. It should be stored under nitrogen.[2]

7. The submitters indicate that N,N-diethylselenourea may be prepared similarly, using diethylcyanamide. In this case, a solution of 50 ml. each of concentrated aqueous ammonium hydroxide and ethanol is used as a solvent. The reaction is carried out at 60°, the solvent being replenished as needed by a solution containing 80 ml. of ethanol and 20 ml. of concentrated ammonium hydroxide. The yield of crude material is 65–80%. Recrystallization from benzene gives a white product, m.p. 117–118°.

8. The procedure gives a commensurate yield when carried out on twice the scale.

9. Iron selenide can be obtained from the Canadian Copper Refiners Ltd., Montreal, Quebec.

3. Methods of Preparation

The procedure used is that of Zingaro, Bennett, and Hammar.[2]

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[1] Camera Works Division, Eastman Kodak Company, Rochester 17, New York.

[2] Zingaro, Bennett, and Hammar, *J. Org. Chem.*, 18, 292 (1953).

ETHYL DIAZOACETATE

(Acetic acid, diazo-, ethyl ester)

$$HCl \cdot NH_2CH_2CO_2C_2H_5 + NaNO_2 \rightarrow N_2CHCO_2C_2H_5 + NaCl + 2H_2O$$

Submitted by N. E. Searle.[1]
Checked by Melvin S. Newman, G. F. Ottmann, and C. F. Grundmann.

1. Procedure

Diazoacetic esters are potentially explosive and therefore must be handled with caution. They are also toxic and prone to cause development of specific sensitivity. A well-ventilated hood should be used for the entire procedure.

A solution of 140 g. (1 mole) of ethyl glycinate hydrochloride[2] in 250 ml. of water is mixed with 600 ml. of methylene chloride in a 2-l. four-necked round-bottomed flask fitted with a stirrer, dropping funnel, thermometer, and nitrogen inlet tube, and cooled to −5° (Note 1). The flask is flushed with nitrogen and an ice-cold solution of 83 g. (1.2 moles) of sodium nitrite in 250 ml. of water is added with stirring. The temperature is lowered to −9° (Note 1), and 95 g. of 5% (by weight) sulfuric acid is added from the dropping funnel during a period of about 3 minutes (Note 2). The temperature may rise to a maximum of +1° with the cooling bath at −23° (Note 3). The reaction terminates within 10 minutes, when heat is no longer evolved.

The reaction mixture is transferred to an ice-cold 2-l. separatory funnel, and the yellow-green methylene chloride layer is run into 1 l. of cold 5% sodium bicarbonate solution. The aqueous layer is extracted once with 75 ml. of methylene chloride. The methylene chloride and sodium bicarbonate solutions are returned to the separatory funnel and shaken until no trace of acid remains, as shown by indicator paper (Note 4). The golden yellow organic layer is separated, transferred to a dry separatory funnel, and shaken for 5 minutes with 15 g. of granular anhydrous sodium sulfate. The dried ethyl diazoacetate solution is filtered through a cotton plug inserted in the separatory funnel stem, and the bulk of the solvent is distilled through an efficient column at a pressure of about 350 mm. (Note 5). The last traces of solvent are removed at a pressure of 20 mm. and a maximum pot temperature of 35° (Note 6). The yield is 90–100 g. (79–88%) of yellow oil, n_D^{25} 1.462. This product is pure enough for most synthetic work (Notes 7 and 8).

2. Notes

1. Lower temperatures may induce the solid methylene chloride dihydrate to separate and interfere with stirring. An acetone bath into which lumps of Dry Ice are introduced as required affords easily controlled cooling.

2. The stated amount of acid has been found sufficient to provide the strongly acidic medium which the reaction requires.

3. Higher reaction temperatures may result in reduced yields.

4. Traces of acid must be eliminated before the diazoacetate solution is concentrated.

5. Efficient solvent separation is indicated by absence of yellow color in the distillate. An 18-in. column packed with Berl saddles is satisfactory.

6. Higher temperatures should be avoided because of the explosive character of ethyl diazoacetate. The product should be placed in dark brown bottles and kept in a cool place. It should be used as soon as possible.

7. Distillation through a 7-in. column packed with glass helices gives a 65% over-all yield, b.p. 29–31°/5 mm. *Anal.* Calcd. for $C_4H_6N_2O_2$: N, 24.55. Found: N, 24.76. Heart-cut material has a refractive index of n_D^{25} 1.4616.[3] Principal loss is due to elimination of nitrogen with formation of high-boiling esters. Both the crude and the distilled products appear to function equally well as synthetic intermediates. *Distillation, even under reduced pressure, is dangerous, for the substance is explosive.*

8. The procedure has proved satisfactory for the preparation of the methyl, butyl, *n*-hexyl, 2-ethylhexyl, and decyl esters of diazoacetic acid.[5] *The methyl ester should be handled with particular caution since heat causes it to detonate with extreme violence.*

3. Methods of Preparation

Ethyl diazoacetate has been prepared from sodium nitrite and ethyl glycinate hydrochloride in the presence of diethyl ether.[4] The present procedure utilizes the unique ability of methylene chloride solvent to protect the diazoacetic ester from decomposition by aqueous mineral acid.[5]

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[1] Contribution No. 360 from the Chemical Department, Experimental Station, E. I. duPont de Nemours and Company, Wilmington, Delaware.

[2] Marvel, *Org. Syntheses*, Coll. Vol. **2**, 310 (1943).

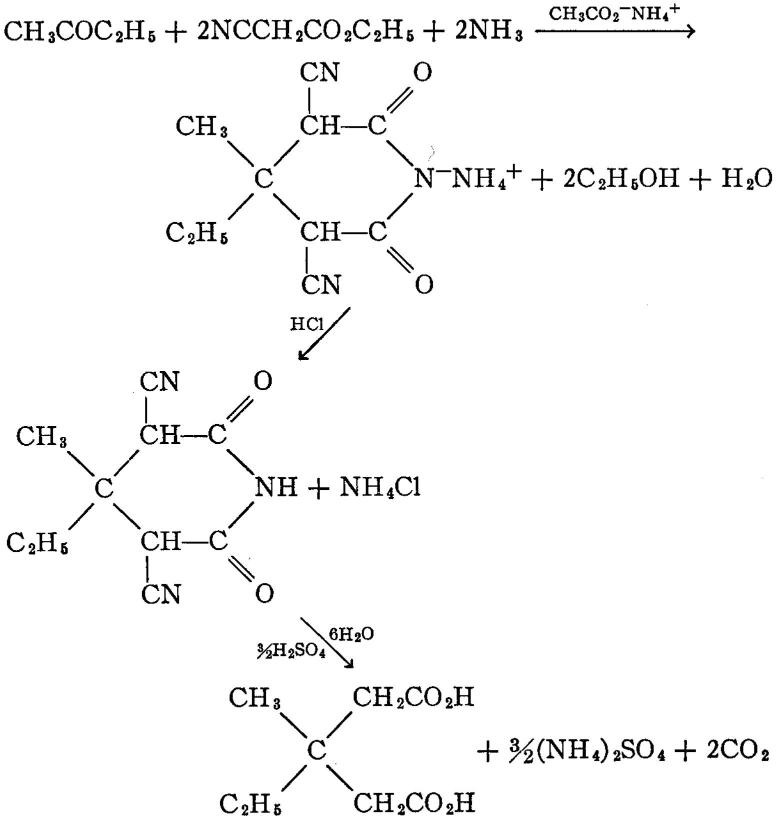
[3] Data obtained by V. A. Engelhardt and H. E. Cupery.[1]

[4] Womack and Nelson, *Org. Syntheses*, Coll. Vol. **3**, 392 (1955).

[5] Searle (to E. I. duPont de Nemours and Company), U. S. pat. 2,490,714 [*C. A.*, **44**, 3519 (1950)].

β-ETHYL-β-METHYLGLUTARIC ACID

(Glutaric acid, 3-ethyl-3-methyl-)



Submitted by H. H. Farmer and Norman Rabjohn.[1]
Checked by Melvin S. Newman and Robert Harper.

1. Procedure

A. *α,α′-Dicyano-β-ethyl-β-methylglutarimide.* In a 2-l. round-bottomed flask are placed 452 g. (4.0 moles) of ethyl cyanoacetate, 144 g. (2.0 moles) of methyl ethyl ketone, 2 g. of ammonium acetate, and 800 ml. of 95% ethanol which contains 80 g. (4.7 moles) of anhydrous ammonia (Notes 1 and 2). The flask is stoppered and placed in a refrigerator.

After about 12 hours, the ammonium salt of the imide which has precipitated is removed by filtration (Note 3), washed on a Büchner funnel with about 200 ml. of ether and air-dried. It is dissolved in the minimum amount (about 800 ml.) of boiling water, and the solution is made acid to Congo red paper with concentrated hydrochloric acid. The free imide precipitates immediately and forms a white slurry which is cooled in an ice bath. The imide is collected on a Büchner funnel and dried at 100° in an oven, or in a vacuum desiccator. The yield is 266–287 g. (65–70%), m.p. 187–191° (Note 4).

B. *β-Ethyl-β-methylglutaric acid.* A mixture of 280 g. (1.36 moles) of α,α′-dicyano-β-ethyl-β-methylglutarimide (Note 5) and 1.35 l. of 65% (by weight) sulfuric acid is heated under reflux in a 5-l. round-bottomed flask for 8–10 hours (Note 6). The mixture is allowed to cool, and the precipitate is removed by filtration on a sintered glass (or other suitable type) filter. The crude β-ethyl-β-methylglutaric acid is recrystallized from water (Note 7). The yield of product is 174–191 g. (73–80%), m.p. 78–80°.

2. Notes

1. The ethyl cyanoacetate and methyl ethyl ketone were Eastman Kodak Company white label grade chemicals and were used without further purification. Commercial absolute ethanol was found to give a slightly better yield of the ammonium salt of the imide.

2. It is convenient to pass gaseous ammonia into the ethanol. It is advisable to carry out the preparation and manipulation of the ammonia solution in a hood.

3. The mother liquor is returned to the refrigerator and a second and a third crop of crystals may be collected after 24 and

48 hours. The first crop of crystals usually comprises 95% of the total yield.

4. In taking the melting point of this compound there was still some solid remaining at 200°. The crude imide is satisfactory for conversion to β-ethyl-β-methylglutaric acid and need not be dried before hydrolysis.

5. Although the ammonium salt of the imide may be hydrolyzed to the acid, the free imide appears to give better results.

6. The large flask is used because considerable foaming occurs during the first 2–3 hours of reaction.

7. A ratio of 3 ml. of water to 1 g. of acid gives satisfactory results. The use of activated carbon during the recrystallization is recommended.

3. Methods of Preparation

α,α′-Dicyano-β-ethyl-β-methylglutarimide apparently has been prepared only from the condensation of methyl ethyl ketone, ethyl cyanoacetate, and ammonia.[2–6]

β-Ethyl-β-methylglutaric acid has been prepared by the acid hydrolysis of α,α′-dicyano-β-ethyl-β-methylglutarimide,[2–6] 3-cyano-4-ethyl-6-imino-2-keto-4-methylpiperidine-5-carboxamide or the diimide of β-ethyl-β-methylpropane-α,α,α′,α′-tetracarboxylic acid;[7] by the oxidation of β-ethyl-β-methyl-δ-valerolactone with chromic acid;[8] and by the reaction of sodium hypobromite on 1,4-dimethyl-1-ethyl-3,5-cyclohexanedione.[9]

The present procedure is essentially that of Guareschi[2] as detailed by Vogel.[4]

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[1] University of Missouri, Columbia, Missouri.

[2] Guareschi, *Atti. accad. sci. Torino*, **36**, 443 (1900–1901) [*Chem. Zentr.*, **1901**, **I**, 821].

[3] Kon and Thorpe, *J. Chem. Soc.*, **115**, 686 (1919).

[4] Vogel, *J. Chem. Soc.*, **1934**, 1758.

[5] Benica and Wilson, *J. Am. Pharm. Assoc.*, **39**, 451 (1950).

[6] Lukeš and Ferles, *Collection Czechoslov. Chem. Communs.*, **16**, 252; *Chem. Listy*, **45**, 386 (1951) [*C. A.*, **47**, 5870 (1953)].

[7] Thole and Thorpe, *J. Chem. Soc.*, **99**, 422 (1911).

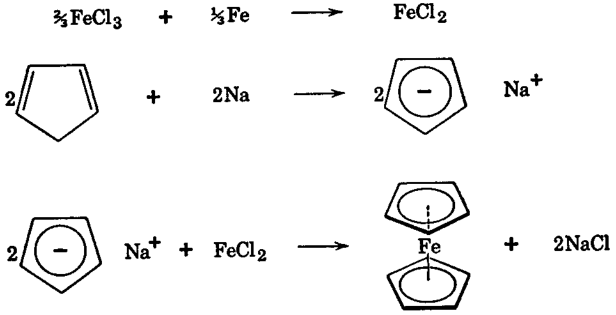
[8] Sircar, *J. Chem. Soc.*, **1928**, 898.

[9] Becker and Thorpe, *J. Chem. Soc.*, **121**, 1303 (1922).

FERROCENE

(Iron, dicyclopentadienyl-)

I. METALLIC SODIUM METHOD



Submitted by G. Wilkinson.[1]
Checked by N. J. Leonard, Kenneth L. Rinehart, Jr., Donald J. Casey, and Sung Moon.

1. Procedure

In a 250-ml. three-necked flask, fitted with a mechanical stirrer, a reflux condenser, and an inlet for admission of nitrogen, is placed 100 ml. of tetrahydrofuran (Note 1). With stirring, 27.1 g. (0.166 mole) of anhydrous ferric chloride is added in portions, followed by 4.7 g. (0.084 gram atom) of iron powder (Note 2). The mixture is heated with stirring under nitrogen at the reflux temperature for 4.5 hours, giving a gray powder with a brown supernatant liquid.

During this time, a second system is assembled, consisting of a 500-ml. three-necked flask fitted with a mechanical stirrer, a reflux condenser topped with a calcium chloride-filled drying tube attached to a xylene-filled bubbler, and a pressure-equalizing dropping funnel through which a slow stream of nitrogen is passed into the flask. In the flask are placed 200 ml. of sodium-dried xylene and 11.5 g. (0.5 gram atom) of sodium. The mixture is heated to boiling, and the sodium is finely dispersed by rapid stirring (Note 3). Stirring is continued while the mixture is allowed to cool in a nitrogen atmosphere. The cooled mixture is allowed to settle, and the bulk of the xylene is siphoned. Tetrahydrofuran (200 ml.) (Note 1) is added through the separatory funnel, and to the stirred mixture, cooled in ice, is added 42 ml. (0.5 mole) of cyclopentadiene (Note 4) in portions during 1 hour (Note 5). Stirring is continued for 2–3 hours in the cold, after which only a small amount of sodium remains unreacted.

The cooled contents of the 250-ml. flask containing ferrous chloride (Note 6) are added to the cold sodium cyclopentadienide solution while passing a stream of nitrogen through both flasks. The combined mixture is stirred for 1.25 hours at a temperature just below reflux. Solvent is removed by distillation, and the ferrocene is extracted from the residue with several portions of refluxing petroleum ether (b.p. 40–60°). The product is obtained by evaporation of the petroleum ether solution. Ferrocene may be purified by recrystallization from pentane or cyclohexane (hexane, benzene, and methanol have also been used) or by sublimation. The yield is 31–34 g. (67–73%) (Note 7), m.p. 173–174°.

2. Notes

1. Tetrahydrofuran may be purified by refluxing over solid potassium hydroxide, followed by distillation from lithium aluminum hydride. Tetrahydrofuran may be replaced by ethylene glycol dimethyl ether (dimethoxyethane). The submitter has indicated that either solvent may be freed conveniently from water, alcohols, and moderate amounts of peroxides by passing the commercial solvent through a column (2 in. diameter × 2–3 ft. length) of Linde Air Products "Molecular Sieves" (type 13A $\frac{1}{16}$-in. pellets), at a rate of approximately 100 ml. per minute.

2. The quality of the iron used in preparing the ferrous chloride has a marked effect on the yield of ferrocene. The checkers employed Rascher and Betzold (730 N. Franklin, Chicago, Ill.) 300-mesh iron powder, reduced by hydrogen. When 40-mesh iron filings were used, the yield of ferrocene was much lower (ca. 33%).

3. The checkers employed a "Mixmaster"-type motor and a Hershberg stirrer made from tantalum wire.

4. Cyclopentadiene, b.p. 40°, is obtained by heating commercial 85% dicyclopentadiene (e.g., from Matheson, Coleman and Bell Company, Norwood, Ohio) under a short column ($\frac{3}{4}$ in. diameter × 8–12 in. length) filled with glass helices. The distilled cyclopentadiene is collected in a receiver which is maintained at Dry Ice temperature until the cyclopentadiene is used. Methylcyclopentadiene and other substituted cyclopentadienes such as indene may also be employed for the synthesis of the correspondingly substituted ferrocenes. In these cases, the reaction of the hydrocarbon with sodium is much slower than with cyclopentadiene, and refluxing for several hours is required to complete the reaction.

5. Under the best conditions, sodium cyclopentadienide gives pale yellow or orange solutions. Traces of air lead to red or purple solutions, as does insufficiently purified solvent, without, however, lowering the reaction yield appreciably. If 1,2-dimethoxyethane is used, in which sodium cyclopentadienide is less soluble than in tetrahydrofuran, white crystals may be obtained at this point.

6. Ferrous chloride may be substituted by ferric chloride directly, with a corresponding reduction in yield, since the sodium cyclopentadienide solution will reduce ferric chloride.

7. The submitter reported yields up to 90% by this method.

3. Methods of Preparation

The methods of preparation of ferrocene have been reviewed by Pauson[2] and by Fischer.[3] Ferrocene has been made by the reaction of ferric chloride with cyclopentadienylmagnesium bromide,[4] by the direct thermal reaction of cyclopentadiene with iron metal,[5] by the direct interaction of cyclopentadiene with iron carbonyl,[6] by the reaction of ferrous chloride with cyclopentadiene in the presence of organic bases such as diethylamine,[7] by the reaction of ferrous chloride with sodium cyclopentadienide in liquid ammonia,[8] and from cyclopentadiene and ferrous acetylacetone–dipyridine complex.[9] The method described here is based upon that developed by Wilkinson and his co-workers for ferrocene and many analogous compounds.[10]

[1] Department of Chemistry, Harvard University, Cambridge, Massachusetts; Imperial College of Science and Technology, London, England.

[2] Pauson, *Quarterly Revs.*, **9**, 391 (1955).

[3] Fischer, *Angew. Chem.*, **67**, 475 (1955).

[4] Kealy and Pauson, *Nature*, **168**, 1039 (1951).

[5] Miller, Tebboth, and Tremaine, *J. Chem. Soc.*, **1952**, 632.

[6] Wilkinson, *J. Am. Chem. Soc.*, **76**, 209 (1954); Piper, Cotton, and Wilkinson, *J. Inorg. Nuclear Chem.*, **1**, 165 (1955); Hallam, Mills, and Pauson, *J. Inorg. Nuclear Chem.*, **1**, 313 (1955).

[7] Birmingham, Seyferth, and Wilkinson, *J. Am. Chem. Soc.*, **76**, 4179 (1954); see Method II, following.

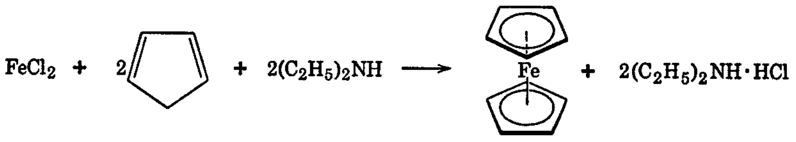
[8] Fischer and Jira, *Z. Naturforsch.*, 8b, 217 (1953); see also Weinmayr, *J. Am. Chem. Soc.*, **77**, 3012 (1955); Ziegler, Froitzheim-Kühlhorn, and Hafner, *Chem. Ber.*, **89**, 434 (1956).

[9] Wilkinson, Pauson, and Cotton, *J. Am. Chem. Soc.*, **76**, 1970 (1954).

[10] Wilkinson and Birmingham, *J. Am. Chem. Soc.*, **76**, 4281 (1954); Wilkinson and Cotton, *Chemistry & Industry*, **1954**, 307; Birmingham, Fischer, and Wilkinson, *Naturwissenschaften*, **42**, 96 (1955); Wilkinson, Cotton, and Birmingham, *J. Inorg. Nuclear Chem.*, **2**, 95 (1956); Cotton and Wilkinson, *Z. Naturforsch.*, **9b**, 417 (1954); Wilkinson, *J. Am. Chem. Soc.*, **74**, 6146 (1952); Wilkinson, *J. Am. Chem. Soc.*, **74**, 6148 (1952); Cotton, Whipple, and Wilkinson, *J. Am. Chem. Soc.*, **75**, 3586 (1953); Wilkinson and Birmingham, *J. Am. Chem. Soc.*, **76**, 6210 (1954); Pauson and Wilkinson, *J. Am. Chem. Soc.*, **76**, 2024 (1954).

II. DIETHYLAMINE METHOD

$$\tfrac{2}{3}FeCl_3 + \tfrac{1}{3}Fe \longrightarrow FeCl_2$$



Submitted by G. Wilkinson.[1]
Checked by N. J. Leonard, Kenneth L. Rinehart, Jr., and Peter Woo.

1. Procedure

The conditions given in the preceding preparation are used for obtaining a suspension of 0.25 mole of ferrous chloride in 100 ml. of tetrahydrofuran (Note 1), contained in a 250-ml. flask. The tetrahydrofuran is then removed under reduced pressure until the residue is almost dry. The flask is cooled in an ice bath, and to the residue is added a mixture of 42 ml. (0.5 mole) of cyclopentadiene and approximately 100 ml. (about 1 mole) of diethylamine. The mixture is stirred vigorously at room temperature for 6–8 hours or, conveniently, overnight. The excess amine is removed under reduced pressure, and the residue is extracted repeatedly with refluxing petroleum ether. The extract is filtered hot, and the solvent is evaporated to leave ferrocene. The product is purified by recrystallization from pentane or cyclohexane or by sublimation. The yield is 34–39 g. (73–84%), m.p. 173–174°.

2. Notes

1. All precautions with regard to the purification of tetrahydrofuran, the quality of the iron powder, the rapid stirring, the maintenance of a nitrogen atmosphere, and the handling of cyclopentadiene, described in the preceding preparation, are followed.

3. Methods of Preparation

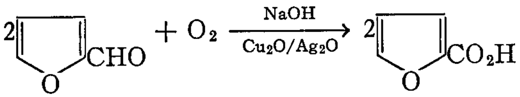
Although not so generally applicable for the preparation of dicyclopentadienyl metal compounds as the sodium cyclopentadienide method, the amine procedure represents the simplest preparation of ferrocene. The amine procedure can also be employed for dicyclopentadienylnickel (about 80% yield), using nickel bromide obtained by the action of bromine on nickel metal powder and 1,2-dimethoxyethane as the solvent. The method of preparation given here is a modified version[2] of that originally described.[3]

[1] Department of Chemistry, Harvard University, Cambridge, Massachusetts; Imperial College of Science and Technology, London, England.

[2] Wilkinson, Cotton, and Birmingham, *J. Inorg. Nuclear Chem.*, **2**, 95 (1956).

[3] Birmingham, Seyferth, and Wilkinson, *J. Am. Chem. Soc.*, **76**, 4179 (1954).

2-FUROIC ACID



Submitted by R. J. Harrisson and M. Moyle.[1]
Checked by James Cason and W. N. Baxter.

1. Procedure

A 1-l. flask (Note 1) is fitted with a condenser, an efficient stirrer, two dropping funnels, a thermometer extending well into the flask, and a delivery tube which extends far enough to be below the surface of the stirred liquid.

To the flask is added 250 ml. of a 2.5% solution of sodium hydroxide and a cuprous oxide-silver oxide catalyst (Note 2). In the two dropping funnels are placed, respectively, 96 g. (1.0 mole) of furfural (Note 3) and a solution of 40 g. (1.0 mole) of sodium hydroxide in 100 ml. of water. The contents of the flask are heated to about 55°, vigorous stirring is started, and a rapid stream of oxygen is bubbled through as the contents of the two funnels are added simultaneously (Note 4) to the reaction mixture at such a rate (20–25 min.) as to maintain the temperature at 50–55° (Note 5) without external heating. After the additions have been completed, vigorous stirring and passage of oxygen are continued until the temperature drops below 40° (15–30 min., depending on the rate of oxygen flow).

The catalyst is separated by filtration, and the aqueous solution is extracted with three 30-ml. portions of ether (Note 6), acidified with 30% sulfuric acid, boiled for 45 min. (Note 7) with 6–7 g. of carbon, then filtered hot. The filtrate is cooled to 0° and allowed to stand at this temperature for 1 hour or longer. The 2-furoic acid, which separates as pale pink needles, m.p. 130–132°, is collected by suction filtration and washed with small portions of ice water (Note 8). The yield is 96–101 g. (86–90%).

2. Notes

1. Since oxygen is passed through the solution at 55°, it is best to operate under a reflux condenser. Ground joint fittings are not essential but convenient. The checkers used a 4-necked flask with ground joints; the thermometer was hung through the condenser, and one neck was arranged for attachment of the gas delivery tube and one of the separatory funnels.

2. The catalyst used is commercial cuprous oxide (9.6 g., 10% of the weight of the furfural) and commercial silver nitrate (0.5 g., 0.5% of the weight of the furfural) in 15 ml. of water. The cuprous oxide is suspended in the rapidly stirred 2.5% sodium hydroxide solution, and the solution of silver nitrate is added to give a dark brown suspension of cuprous oxide and silver oxide which is used directly. So long as oxygen is being passed through the reaction mixture, the life of the catalyst appears to be unlimited.

3. A sample of commercial furfural is purified by simple distillation or steam distillation immediately before use. The submitters have carried out this reaction on an 8-mole scale following the same procedure except that a total reaction time of about 4 hours was required.

4. The simultaneous addition of furfural and sodium hydroxide maintains the concentration of sodium hydroxide at about 2.5%, at which concentration only a small percentage of furfuryl alcohol is formed in the accompanying Cannizzaro reaction.

5. Below 50°, the reaction is too slow; above 55°, the reaction becomes violent and cooling becomes necessary. Frothing may be checked by addition of small amounts of benzene.

6. Ether extraction at this stage removes furfuryl alcohol (about 12 g.). If this is not removed, the reaction mixture becomes resinous on acidification and heating.

7. During the period of boiling in acid solution a small amount of polymeric material forms, and this is separated when the charcoal is removed by filtration.

8. The solubility of 2-furoic acid in water is 2.8 g. per 100 ml. at 0°; however, its solubility in the salt solution resulting from

the reaction is quite low. Usually it is not possible to obtain further material from the filtrate by salting out with sodium chloride; however, in case a lowered yield is obtained in the first crop it may be profitable to investigate the possibility of obtaining additional material from the filtrate.

3. Methods of Preparation

2-Furoic acid has been made by oxidation of lactose followed by pyrolysis, by the oxidation of 2-acetylfuran, 2-methylfuran, or furfuryl alcohol using potassium ferricyanide in alkaline medium, and by other methods already listed.[2]

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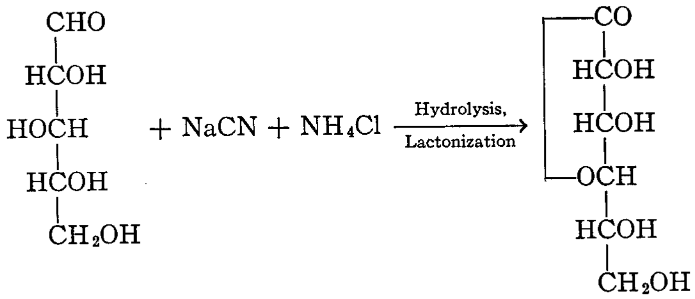
[1] Department of Organic Chemistry, University of Sydney, Sydney, Australia.

[2] Wilson, *Org. Syntheses*, Coll. Vol. 1, 276 (1941).

D-GULONIC-γ-LACTONE

(D-Gulonic acid, γ-lactone)



Submitted by J. V. Karabinos.[1]
Checked by R. T. Arnold, Fred Smith, and Bertha Lewis.

1. Procedure

In a 500-ml. glass-stoppered Erlenmeyer flask, 30 g. (0.2 mole) of D-xylose and 10.7 g. (0.2 mole) of ammonium chloride are dissolved in 100 ml. of distilled water. Cracked ice (100 g.) is added to this mixture, followed by 10 g. (0.2 mole) of sodium cyanide, and the solution is maintained at 0–5° for 48 hours.

Powdered barium hydroxide octahydrate (63 g., 0.2 mole) is added along with 100 ml. of water to the cyanohydrin mixture (Note 1), which is heated on a steam bath for 2 hours with occasional stirring. The basic barium gulonate (Note 2), which is allowed to separate overnight at 5°, is collected by filtration and washed with cold water (0°) until the washings are chloride-free. Excessive washing of the barium salt is to be avoided because of its solubility. The barium salt is suspended in 200 ml. of water, and the barium ion is precipitated quantitatively by sulfate ion (Note 3). After removal of the barium sulfate by suction filtration, the filtrate and washings are concentrated to a colorless syrup on a steam bath in a stream of dry air (Note 4). The resultant syrup is dissolved in 50 ml. of hot ethylene glycol monomethyl ether (Methyl Cellosolve), sufficient ethyl acetate is added to incipient turbidity, and the solution is seeded with D-gulonic-γ-lactone (Note 5). The lactone, which is allowed to crystallize overnight, is collected by suction filtration, washed with ethanol and dried in a vacuum oven at 60°. The D-gulonic-γ-lactone (Note 6) has a melting point of 181–183° which is unchanged by recrystallization from aqueous ethanol. The yield is 10.7–11.6 g. (30–33%) (Note 7).

2. Notes

1. The barium hydroxide serves to hydrolyze any unchanged nitriles as well as to precipitate the aldonic acid.

2. The barium gulonate is undoubtedly contaminated with some epimeric idonate. The lactone of the latter substance is removed by recrystallization of the gulonic lactone from Methyl Cellosolve.

3. It is convenient to titrate the suspended barium salt with 18 *N* sulfuric acid (approx. 12–14 ml.) to a *p*H of 1.5 using a *p*H meter. After removal of the barium sulfate the slight excess of sulfate ion may be precipitated using barium chloride solution. The end point is taken when several drops of filtrate show no turbidity either upon addition of sulfuric acid or barium chloride solution.

4. Concentration in this manner allows sufficient time for the gulonic acid to be converted to the lactone in the presence of a trace of hydrochloric acid. The checkers observed also that an easily crystallized lactone was always obtained if concentration *in vacuo* were employed.

5. Crystallization is speeded considerably by seeding.

6. A small amount of less pure lactone may be obtained by evaporation of the mother liquor to a syrup and repetition of the Methyl Cellosolve-ethyl acetate crystallization.

7. The submitter has reported yields up to 39% using the above procedure.

3. Methods of Preparation

The present method is adapted from Fischer[2] employing recently developed modifications of the cyanohydrin synthesis.[3,4]

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[1] Blockson Chemical Company, Joliet, Illinois.

[2] Fischer and Stahel, *Ber.*, **24**, 528 (1891).

[3] Karabinos, Hann, and Hudson, *J. Am. Chem. Soc.*, **75**, 4320 (1953).

[4] Isbell, Karabinos, Frush, Holt, Schwebel, and Galkowski, *J. Research Natl. Bur. Standards*, **48**, 163 (1952).

n-HEXYL FLUORIDE

(Hexane, 1-fluoro-)

$$CH_3(CH_2)_4CH_2Br + KF \xrightarrow{\text{Ethylene glycol}} CH_3(CH_2)_4CH_2F + KBr$$

Submitted by Arthur I. Vogel, James Leicester, and William A. T. Macey.[1]
Checked by T. L. Cairns and C. W. Tullock.

1. Procedure

In a thoroughly dry 500-ml. three-necked round-bottomed flask, equipped with a mercury-sealed stirrer, a 100-ml. dropping funnel and a short fractionating column (Note 1), is placed a mixture of 116 g. (2.0 moles) of anhydrous finely powdered potassium fluoride (Note 2) and 200 g. of dry ethylene glycol (Note 3). The fractionating column carries a thermometer and is connected to a downward double-surface condenser with a filter flask as receiver. The round flask is heated at a bath temperature of 160–170°, and 165 g. (1.0 mole) of *n*-hexyl bromide, b.p. 154–156° (Note 4), is added dropwise during 5 hours; liquid passes over intermittently at 60–90° (temperature at the top of the fractionating column). The bath temperature is allowed to fall to 110–120°, and a slow stream of air is drawn through the apparatus by attaching the side arm of the filter flask to a water pump and replacing the dropping funnel by a narrow-bore tube dipping just below the surface of the liquid; stirring is maintained during this operation. It is advisable to interpose a U-tube cooled in ice between the water pump and the receiver in order to recover any uncondensed liquid. The combined distillates are then distilled at atmospheric pressure through an efficient fractionating column; after a small fore-run (up to 10 g.) of 1-hexene, the crude *n*-hexyl fluoride is collected at 89–92° (46–48 g.). The crude product is purified by cooling in ice and adding 1-ml. portions of a solution containing 9.0 g. of bromine and 6.0 g. of potassium bromide in 50 ml. of water until the organic layer acquires an orange color; after each addition the mixture is shaken vigorously for a minute or so. The volume of bromine-potassium bromide solution required is usually less than 5 ml. The aqueous layer is separated, the organic layer is washed with saturated aqueous potassium bromide solution until colorless and finally with water. The liquid is dried with anhydrous magnesium sulfate and distilled through an efficient fractionating column; the *n*-hexyl fluoride is collected at 91–92°. This procedure yields 42–47 g. (40–45% over-all yield based on the bromide employed) of a water-white product, n_D^{20} 1.375, n_D^{25} 1.372–1.373, d_4^{20} 0.8011. It has been kept for 1 year without change of physical properties and therefore appears to be stable (Note 5).

2. Notes

1. Any fractionating column of moderate efficiency is satisfactory. The submitters employed a 20-cm. Dufton column

containing a spiral 10 cm. in length, 2 cm. in diameter, with 8 turns of the helix. A 20–25 cm. Vigreux column may also be used.

2. Pure laboratory-grade anhydrous potassium fluoride is finely ground and kept for 48 hours in an oven at 180–210°; it is stored in a desiccator. Before use, the powdered salt is dried for 3 hours at 180° and ground again in a warm (50°) glass mortar.

3. Laboratory-grade ethylene glycol is redistilled under diminished pressure, and the fraction boiling at 85–90°/7 mm. is used as the solvent for the potassium fluoride.

4. The *n*-hexyl bromide may be prepared from redistilled *n*-hexyl alcohol by the red phosphorus-bromine procedure or may be purchased from Eastman Kodak Company.

5. The procedure described has been employed by the submitters for the preparation of the alkyl fluorides listed below. Due regard must be paid to the boiling point of the alkyl bromide; as a general rule the bath temperature is maintained at about the boiling point of the alkyl bromide, with a minimum value (for *n*-amyl fluoride) of about 140–150°. For bromides of higher boiling point, the bath temperature is held at about 190°. In all cases, after the alkyl bromide has been added, the bath is allowed to cool 10–20° below the original reaction temperature, and a slow stream of air is drawn through the apparatus; the alkyl fluoride and ethylene glycol which pass over are collected, and the latter is removed by washing with water.

Alkyl fluoride	B.p.	d_4^{20}	n_D^{20}	n_D^{25}	Yield
n-Amyl	63.5–65°	0.7917	1.3597	1.3562	27%
n-Heptyl	119–121°	0.8060	1.3861	1.3833	35%
n-Octyl	144–146°	0.8137	1.3955	1.3927	34%
n-Nonyl	166–169°	0.8159	1.4033	1.4002	46%
n-Decyl	186–188°	0.8197	1.4095	1.4068	37%
n-Undecyl	70–71.5°/3 mm.	0.8239	1.4151	1.4122	45%
n-Dodecyl	93–95°/3 mm.	0.8257	1.4192	1.4162	34%
n-Tetradecyl	119–121°/3 mm., m.p. 8°	0.8277	1.4266	1.4236	43%
n-Hexadecyl	150–152°/2 mm., m.p. 19°	0.8313	1.4322	1.4295	27%

3. Methods of Preparation

Alkyl fluorides have been prepared by reaction between elementary fluorine and the paraffins,[2] by the addition of hydrogen fluoride to olefins,[3] by the reaction of alkyl halides with mercurous fluoride,[4] with mercuric fluoride,[5] with silver fluoride,[6] or with potassium fluoride under pressure.[7] The procedure used is based on that of Hoffmann [8] involving interaction at atmospheric pressure of anhydrous potassium fluoride with an alkyl halide in the presence of ethylene glycol as a solvent for the inorganic fluoride; a small amount of olefin accompanies the alkyl fluoride produced and is readily removed by treatment with bromine-potassium bromide solution. Methods for the preparation of alkyl monofluorides have been reviewed.[9]

[1] Department of Chemistry, Woolwich Polytechnic, London, S.E. 18, England.

[2] Hadley and Bigelow, *J. Am. Chem. Soc.*, **62**, 3302 (1940).

[3] Grosse and Linn, *J. Org. Chem.*, **3**, 26 (1938); Grosse, Wackher, and Linn, *J. Phys. Chem.*, **44**, 275 (1940).

[4] Swarts, *Bull. classe sci. Acad. roy. Belg.*, **7**, 438 (1921); *Bull. soc. chim. Belg.*, **46**, 10 (1937); Desreux, *Bull. classe sci. Acad. roy. Belg.*, **20**, 457 (1934); *Bull. soc. chim. Belg.*, **44**, 1 (1935); Henne and Renoll, *J. Am. Chem. Soc.*, **60**, 1060 (1938); Vogel, *J. Chem. Soc.*, **1948**, 649.

[5] Henne and Midgley, *J. Am. Chem. Soc.*, **58**, 884 (1936); see also Henne in Adams, *Org. Reactions*, **2**, 57 (1944). Henne and Renoll, *J. Am. Chem. Soc.*, **58**, 887 (1936).

[6] Swarts, *Bull. soc. chim. Belg.*, **30**, 302 (1921).

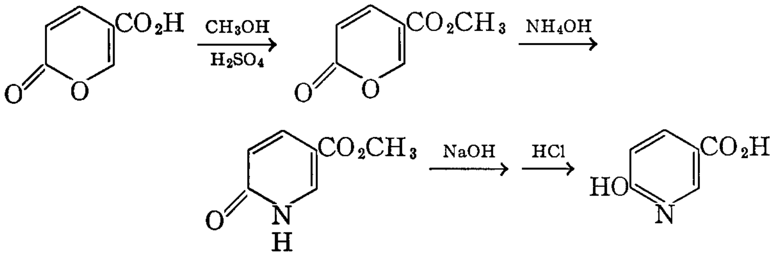
[7] Gryszkiewicz-Trochimowski, Sporzynski, and Wnuk, *Rec. trav. chim.*, **66**, 413 (1947).

[8] Hoffmann, *J. Am. Chem. Soc.*, **70**, 2596 (1948); *J. Org. Chem.*, **14**, 105 (1949); **15**, 425 (1950).

[9] Pattison, *Nature*, **174**, 740 (1954).

6-HYDROXYNICOTINIC ACID

(Nicotinic acid, 6-hydroxy-)



Submitted by J. H. BOYER and W. SCHOEN.[1]
Checked by T. L. CAIRNS and W. J. LINN.

1. Procedure

A. *Methyl coumalate.* In a 500-ml. round-bottomed flask provided with a thermometer is placed 139 ml. of concentrated sulfuric acid. To the acid is added, with swirling, 50 g. (0.36 mole) of pulverized coumalic acid[2] in small portions. The reaction is slightly exothermic, and the mixture is maintained between 20° and 30° by occasional immersion of the flask into an ice bath. Methanol (70 ml.) is then added in small portions with frequent swirling, and the temperature is held between 25° and 35°. The mixture is heated on a steam bath for 1 hour, cooled to about 40°, and poured slowly with stirring into 800 ml. of water in a 2-l. beaker while the temperature is maintained below 40° by an ice bath (Note 1). Anhydrous sodium carbonate is added in small portions with stirring until the mixture is slightly alkaline (Note 2). The precipitated ester is freed of inorganic salts by slurrying four times with 100-ml. portions of cold water, filtered, and air-dried overnight. The yield of methyl coumalate, m.p. 68–70°, is 17.5–24.5 g. (32–45%). This crude product is used for the preparation of 6-hydroxynicotinic acid.

B. *6-Hydroxynicotinic acid.* In a 500-ml. beaker provided with a thermometer, magnetic stirring, and external cooling is placed 117 ml. of 14% ammonium hydroxide. With stirring,

45 g. (0.29 mole) of methyl coumalate is added over a period of 10 minutes, during which time the solution is kept below 20°. Stirring is continued for an additional 45 minutes at about 20° (Note 3).

A solution of 600 ml. of approximately 17% aqueous sodium hydroxide is placed in a 2-l. beaker and heated almost to the boiling point. At the end of the 45-minute period, the ammoniacal solution is added to the hot sodium hydroxide solution, and the mixture is heated rapidly to the boiling point. After it has boiled vigorously for 5 minutes, the stirred solution is cooled in an ice bath to room temperature. With the temperature held below 30°, concentrated hydrochloric acid is added with stirring until the solution is strongly acid (Note 4). The heavy, yellow, microcrystalline solid which separates after stirring and cooling for about an hour is collected on a Büchner funnel, washed twice with water, and dried at 80°. The yield of bright yellow 6-hydroxynicotinic acid, m.p. 299–300° (dec., uncor.), is 29–37 g. (72–91%) (Note 5).

2. Notes

1. A turbid, brown solution containing a small amount of fine precipitate is obtained.
2. A small amount of curdy, brown precipitate is obtained at first. About 220 g. of anhydrous sodium carbonate is required.
3. Most of the ester dissolves; a turbid, red solution is formed.
4. About 250 ml. of acid is required.
5. The product is sufficiently pure for further synthetic work; a purer product may be obtained by recrystallization from 50% aqueous acetic acid.

3. Methods of Preparation

The procedure for preparing methyl coumalate is based on a method described by von Pechmann.[5] Methyl coumalate has also been prepared by direct esterification of the reaction mixture from malic acid and fuming sulfuric acid[3] and from coumalyl chloride and methanol.[4]

The procedure for preparing 6-hydroxynicotinic acid is also based on a method described by von Pechmann.[6] 6-Hydroxynicotinic acid has also been prepared by decarboxylation of 6-hydroxy-2,3-pyridinedicarboxylic acid;[7,8] by heating 6-hydrazinonicotinic acid or its hydrazide with hydrochloric acid;[9] by the action of carbon dioxide on the sodium salt of α-pyridone at 180–200° and 20 atmospheres;[10] by heating the nitrile of 6-chloronicotinic acid with alcoholic sodium hydroxide or hydrochloric acid;[11] from 6-aminonicotinic acid;[12,13] and by the prolonged action of concentrated ammonium hydroxide on methyl coumalate.[3]

[1] Department of Chemistry, Tulane University, New Orleans, Louisiana.

[2] Wiley and Smith, *Org. Syntheses*, **31**, 23 (1951).

[3] Caldwell, Tyson, and Lauer, *J. Am. Chem. Soc.*, **66**, 1479 (1944).

[4] Wiley and Knabeschuh, *J. Am. Chem. Soc.*, **77**, 1615 (1955).

[5] von Pechmann, *Ann.*, **264**, 279 (1891).

[6] von Pechmann and Welsh, *Ber.*, **17**, 2391 (1884).

[7] Königs and Geigy, *Ber.*, **17**, 589 (1884).

[8] Diamant, *Monatsh. Chem.*, **16**, 767 (1895).

[9] Marckwald and Rudzik, *Ber.*, **36**, 1114 (1903).

[10] Tschitschibabin and Kirssanow, *Ber.*, **57B**, 1162 (1924).

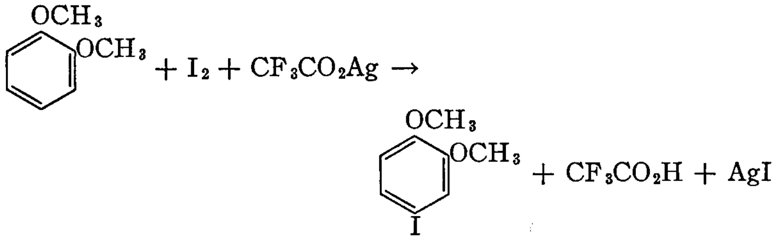
[11] Räth (to Schering-Kahlbaum A.-G.), Ger. pat. 447,303 [*Friedlaender*, **15**, 1487 (1925–1927)].

[12] Marckwald, *Ber.*, **27**, 1323 (1894).

[13] Räth and Prange, *Ann.*, **467**, 9 (1928).

4-IODOVERATROLE

(Veratrole, 4-iodo-)



Submitted by Donald E. Janssen and C. V. Wilson.[1]
Checked by Max Tishler and George Purdue.

1. Procedure

A. *Silver trifluoroacetate.* To a suspension of 187 g. (0.81 mole) of silver oxide (Note 1) in 200 ml. of water is added 177 g. (1.55 moles) of trifluoroacetic acid (Note 2). The resulting solution is filtered, and the filtrate is evaporated to dryness under reduced pressure. The dry silver trifluoroacetate thus obtained is purified by placing it in a Soxhlet thimble and extracting with ether, or by dissolving the salt in 1.2 l. of ether, filtering through a thin layer of activated carbon, and evaporating the filtered ether solution to dryness. The yield of colorless crystalline salt obtained after removal of the ether is 300 g. (88%).

B. *4-Iodoveratrole.* In a 3-l. three-necked round-bottomed flask, fitted with a sealed stirrer, a dropping funnel, and a reflux condenser protected with a drying tube, is placed 110 g. (0.5 mole) of dry silver trifluoroacetate (Note 3). The flask is flamed to remove all moisture, and 69 g. (0.5 mole) of dry veratrole is added (Note 2). To the stirred suspension a solution of 127 g. (0.5 mole) of iodine in 1.6 l. of chloroform is added through the dropping funnel over a period of 2 hours. After stirring an additional hour, the mixture is filtered and the precipitated silver iodide is washed with 100 ml. of chloroform. The solvent is removed from the filtrate and washings under vacuum, and the residue is distilled through an 8-in. Vigreux column. The fraction boiling at 152–155°/15 mm. weighs 112–120 g. and constitutes a yield of 85–91% (Notes 4 and 5).

2. Notes

1. The silver oxide was prepared by adding, with manual stirring, 66 g. of 98% sodium hydroxide (1.62 moles) in 2 l. of water to a solution of 274 g. (1.62 moles) of silver nitrate in 500 ml. of water. The precipitate was collected by filtration and washed with water until free from alkali. The wet cake can be dried or preferably used moist for reaction with trifluoroacetic acid.

2. The trifluoroacetic acid and veratrole used were Eastman Kodak Company white label grade.

3. Commercially available silver acetate may be used in place of the silver trifluoroacetate, but the yield is somewhat lower (75–80%).

4. The product, n_D^{25} 1.612, solidifies on chilling. Recrystallization from ethanol gives solid of melting point 34–35°.

5. Iodination in the presence of mercuric oxide[2,3,4] gives yields of about 40–55%, and even after careful distillation the product is contaminated with mercury salts.

3. Methods of Preparation

4-Iodoveratrole has been prepared by iodination of veratrole in the presence of mercuric oxide[2,3,4] and by methylation of 4-iodoguaiacol with methyl iodide in alcoholic sodium ethoxide solution.[5]

---

[1] Eastman Kodak Company, Rochester 17, New York.

[2] Ritchie, *J. Proc. Roy. Soc. N. S. Wales*, **78**, 134 (1945) [*C. A.*, **40**, 876 (1946)].

[3] Jurd, *Australian J. Sci. Research*, **2A**, 246 (1949) [*C. A.*, **45**, 2887 (1951)].

[4] Seer and Karl, *Monatsh. Chem.*, **34**, 647 (1913).

[5] Tassilly and Leroide, *Compt. rend.*, **144**, 757 (1907); *Bull. soc. chim. France*, [4], **1**, 932 (1907) [*C. A.*, **1**, 1848 (1907)].

LAURYLMETHYLAMINE

(Dodecylamine, N-methyl-)

$$CH_3(CH_2)_{10}CONHCH_3 \xrightarrow{LiAlH_4} CH_3(CH_2)_{10}CH_2NHCH_3$$

Submitted by C. V. Wilson and J. F. Stenberg.[1]
Checked by N. J. Leonard and C. W. Schimelpfenig.

1. Procedure

In a 5-l. three-necked flask, fitted with a ball-joint sealed stirrer and a Soxhlet extractor (70 mm. internal diameter × 300 mm. length of body) carrying a large-capacity condenser, are placed

1.8 l. of dry ether (Note 1) and 38 g. (1 mole) of finely divided lithium aluminum hydride (Note 2). In the Soxhlet cup is placed 160 g. (0.75 mole) (Note 3) of N-methyllauramide (m.p. 67–69°) (Note 4). The mixture is heated under gentle reflux with efficient stirring over a 5-hour period and then stirred overnight at room temperature (Note 5); the N-methyllauramide is extracted from the cup during the first 3 hours.

The excess lithium aluminum hydride and the metallic complexes are decomposed by the careful addition of 82 ml. of distilled water, from a dropping funnel, to the well-stirred mixture. The reaction mixture is stirred for an additional 30 minutes, filtered with suction, and the solid is washed with several 100-ml. portions of ether. After the ether is removed from the filtrates, the residual oil is distilled under reduced pressure. The yield of laurylmethylamine, a colorless liquid boiling at 110–115°/1.2–1.5 mm., is 121–142 g. (81–95%) (Note 6).

2. Notes

1. It is preferable to use ether subjected to final drying by distillation from lithium aluminum hydride.

2. The yield depends upon the use of high-quality, fresh lithium aluminum hydride.

3. If a Soxhlet extractor having a smaller capacity is employed, the cup will have to be recharged during the course of the reaction.

4. N-Methyllauramide, N-methylmyristamide, and N-methylpelargonamide can be prepared in 95–98% yield by adaptation of the method used by Roe, Scanlan, and Swern[2] for the preparation of amides of oleic and 9,10-dihydroxystearic acids.

5. Stirring overnight is a matter of convenience. In the preparation of methylnonylamine, refluxing for an hour after the addition of the amide was found by the submitters to be sufficient.

6. Methylnonylamine and methylmyristylamine were prepared by the submitters in 89–92% yield using the same procedure; with methylmyristylamine a longer reflux period was required, owing to the lower solubility of the amide.

3. Methods of Preparation

Laurylmethylamine has been prepared by the reaction of lauryl alcohol with methylamine under pressure in the presence of catalysts at high temperature,[3] by heating lauryl chloride with methylamine in alcoholic or aqueous medium under pressure,[4, 5, 6] and by the reaction of lauryl halides with aqueous methylamine.[7] Cetylmethylamine has been prepared by the catalytic debenzylation of benzylcetylmethylamine.[8]

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[1] Eastman Kodak Company, Rochester 17, New York.

[2] Roe, Scanlan, and Swern, *J. Am. Chem. Soc.*, **71**, 2215 (1949).

[3] I. G. Farbenindustrie A.-G., Fr. pat. 779,913 [*C. A.*, **29**, 5458 (1935)].

[4] Westphal and Jerchel, *Ber.*, **73B**, 1002 (1940).

[5] Ralston, Reck, Harwood, and DuBrow, *J. Org. Chem.*, **13**, 186 (1948).

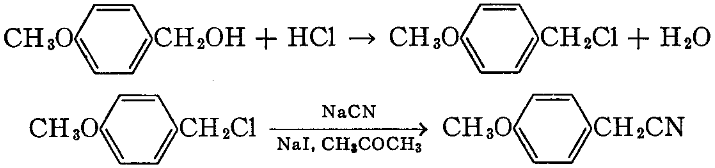
[6] Zerweck and Gofferjé (I. G. Farbenindustrie A.-G.), Ger. pat. 657,35 [*C. A.*, **32**, 4175 (1938)].

[7] I. G. Farbenindustrie A.-G., Fr. pat. 784,599 [*C. A.*, **30**, 107 (1936)].

[8] Birkofer, *Ber.*, **75B**, 429 (1942).

p-METHOXYPHENYLACETONITRILE

(Acetonitrile, *p*-methoxyphenyl-)



Submitted by Kurt Rorig, J. Derland Johnston, Robert W. Hamilton, and Thomas J. Teliński.[1]
Checked by William S. Johnson, Stanley Seltzer, and Peter Yates.

1. Procedure

In a 1-l. flask fitted with a paddle-blade stirrer are placed 138 g. (1 mole) of anisyl alcohol (Note 1) and 248 ml. of concentrated hydrochloric acid. After stirring vigorously for 15 minutes the contents of the flask are transferred to a separatory funnel. The

lower layer (anisyl chloride) is separated, dried over 20 g. of granular calcium chloride for about 30 minutes, and filtered to remove the drying agent.

In a 2-l. three-necked round-bottomed flask, fitted with an efficient sealed stirrer and a reflux condenser capped by a drying tube, are placed the dried anisyl chloride (Notes 2 and 3), 73.6 g. (1.5 moles) of finely powdered sodium cyanide, 10 g. of sodium iodide, and 500 ml. of dry acetone (Note 4). The heterogeneous reaction mixture is heated under reflux with vigorous stirring for 16–20 hours, then cooled and filtered with suction. The solid on the filter is washed with 200 ml. of acetone and discarded (Note 5). The combined filtrates are distilled to remove the acetone. The residual oil is taken up in 300 ml. of benzene and washed with three 100-ml. portions of hot water. The benzene solution is dried over anhydrous sodium sulfate for about 15 minutes, and the solvent is removed by distillation at the reduced pressure of the water aspirator (Note 6). The residual *p*-methoxyphenylacetonitrile is purified by distillation under reduced pressure through an 8-in. Vigreux column; b.p. 94–97°/0.3 mm.; n_D^{25} 1.5285–1.5291. The yield is 109–119 g., or 74–81% based on anisyl alcohol (Notes 7 and 8).

2. Notes

1. Givaudan-Delawanna (330 W. 42nd Street, New York 18, N. Y.) "Anisic Alcohol" of 97% minimum purity was used.

2. The crude anisyl chloride is unstable. It should be used the same day it is made.

3. This step should be performed in a well-ventilated hood.

4. The acetone is dried over about one-quarter its volume of granular calcium chloride for one day. The dried acetone is then filtered and distilled.

5. This residue should be discarded with due regard for the unused sodium cyanide it contains.

6. The undistilled *p*-methoxyphenylacetonitrile weighs 125–139 g. (85–95%) and has a refractive index close to that of the distilled product. It can be used for many purposes, such as

condensation with aromatic aldehydes to yield α-*p*-methoxyphenylcinnamonitriles, without further purification.

7. The submitters have carried out this preparation on five times the scale described here with comparable yields.

8. This method is particularly applicable to the more reactive benzyl halides which are easily hydrolyzed in the aqueous media usually employed for the metathetical reaction with alkali cyanides. For example, anisyl chloride treated with sodium cyanide in aqueous dioxane gives, as a by-product, 5–10% of anisyl alcohol as determined by infrared analysis. The use of anhydrous acetone not only prevents hydrolysis to the alcohol but also decreases the formation of isonitriles. This method was also applied successfully by the submitters to the preparation of *p*-chlorophenylacetonitrile in 74% yield.

3. Methods of Preparation

This method is an adaptation of that of Dengel.[2] *p*-Methoxyphenylacetonitrile can also be prepared by the metathetical reaction of anisyl chloride with alkali cyanides in a variety of aqueous solvent mixtures;[3-9] by the nitration of phenylacetonitrile, followed by reduction, diazotization, hydrolysis, and methylation;[10,11] by the reduction of α-benzoxy-*p*-methoxyphenylacetonitrile (prepared from anisaldehyde, sodium cyanide, and benzoyl chloride);[12] and by the reaction of acetic anhydride with the oxime of *p*-methoxyphenylpyruvic acid.[13]

---

[1] G. D. Searle and Company, Chicago 80, Illinois.

[2] Dengel, German pat. application (DBP, Anm. K2355, March 30, 1950; Knoll-A.G.) as reported by Müller, *Methoden der Organischen Chemie* (Houben-Weyl), Vol. 8, p. 294, Georg Thieme Verlag, Stuttgart, 1952.

[3] Shriner and Hull, *J. Org. Chem.*, **10**, 230 (1945).

[4] Métayer, *Ann. chim. Paris*, [12], **4**, 210 (1949).

[5] Van Heyningen, *J. Am. Chem. Soc.*, **74**, 4862 (1952).

[6] Dankova, Evdokimova, Stepanov, and Preobrazhenskiĭ, *Zhur. Obshcheĭ Khim.*, **18**, 1724 (1948) [*C. A.*, **43**, 2606 (1949)].

[7] Lapiné, *Bull. soc. chim. France*, [5], **6**, 390 (1939).

[8] Lee, Ziering, Berger, and Heineman, *Jubilee Vol. Emil Barell*, **1946**, 280 [*C. A.*, **41**, 6252 (1947)].

[9] Livshits, Bazilevskaya, Bainova, Dobrovinskaya, and Preobrazhenskiĭ, *Zhur. Obshcheĭ Khim.*, **17**, 1675 (1947) [*C. A.*, **42**, 2606 (1948)].

[10] Pschorr, Wolfes, and Buckow, *Ber.*, **33**, 171 (1900).

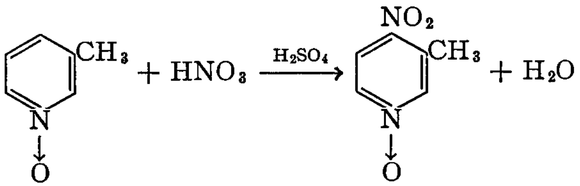
[11] Silverman and Bogert, *J. Org. Chem.*, **11**, 43 (1946).

[12] Campbell and McKail, *J. Chem. Soc.*, **1948**, 1255.

[13] Baker and Eastwood, *J. Chem. Soc.*, **1929**, 2902.

3-METHYL-4-NITROPYRIDINE-1-OXIDE

(3-Picoline, 4-nitro-, 1-oxide)



Submitted by E. C. Taylor, Jr.,[1] and Aldo J. Crovetti.[2]
Checked by Max Tishler and Henry B. Lange.

1. Procedure

One hundred and eighty grams (1.65 moles) of liquefied 3-methylpyridine-1-oxide (Note 1) is added to 630 ml. of cold (0–5°) sulfuric acid (sp. gr. 1.84) contained in a 3-l. round-bottomed flask immersed in an ice-salt bath. The resulting mixture is cooled to about 10°, and 495 ml. of fuming yellow nitric acid (sp. gr. 1.50) is added in 50-ml. portions with shaking. An efficient spiral condenser (52 × 4 cm.) is attached to the flask, and the latter is placed in an oil bath. The temperature is slowly raised to 95–100° during 25–30 minutes, at which time gas evolution begins. After about 5 minutes the rate of gas evolution increases, and the oil bath is removed. A spontaneous and vigorous reaction commences which must be controlled by the application of an ice-water bath (Note 2). After the vigorous reaction has subsided to a moderate rate (about 5 minutes) the ice-water bath is removed, and the reaction is allowed to proceed for an additional 5–10 minutes. The oil bath is then replaced, and heating is continued at 100–105° for 2 hours.

The reaction mixture is cooled to 10° and poured onto 2 kg. of crushed ice contained in a 4-l. beaker. Addition of 1.36 kg. of sodium carbonate monohydrate (Hood!)(Note 3) in small portions with stirring causes the separation of the yellow crystalline product along with sodium sulfate. The mixture is then allowed to stand for 3 hours to expel nitrogen oxides. The yellow solid is collected by suction filtration, thoroughly washed with water, and rendered as dry as possible on the filter. The filtrates (about 4 l.) are transferred to a separatory funnel.

The collected solid is extracted twice with 400–500 ml. portions of boiling chloroform, the combined extracts are used to extract the aqueous filtrates contained in the separatory funnel, and the extraction is repeated with several fresh 500-ml. portions of chloroform. The combined chloroform extracts are then given preliminary drying over anhydrous sodium sulfate and evaporated to dryness by distillation under reduced pressure. The residue is transferred to a 2-l. Erlenmeyer flask and dissolved in 1.5 l. of boiling acetone. The acetone solution is concentrated on a steam bath to 800–900 ml. (crystallization begins when the volume is about 1 l.) and then cooled at 5° for 6–8 hours. The product is filtered by suction, the filtrates are removed and saved, and the collected solid is washed with ether and dried. The yield is 162–173 g. (64–68%), m.p. 137–138°. The acetone filtrates mentioned above are boiled down to 150 ml. and chilled in an ice bath, and the crude product so obtained (m.p. 131–135°) is recrystallized from acetone to give an additional 13.5–16.5 g., m.p. 136–138°. The total yield is 178–187 g. (70–73%).

2. Notes

1. Freshly distilled 3-methylpyridine-1-oxide (b.p. 101–103°/0.7–0.8 mm.) will remain in a supercooled liquid state for several hours before solidifying. The highly hygroscopic solid may be melted on a steam bath in a tightly closed, previously weighed flask, and the melt poured slowly into the sulfuric acid. A large amount of heat is liberated in the mixing.

3-Methylpyridine-1-oxide (3-picoline-1-oxide) may be prepared by a method similar to that employed for pyridine-1-oxide.[3] To a mixture of 600–610 ml. of glacial acetic acid and

200 g. (2.15 moles) of freshly distilled 3-methylpyridine (b.p. 141–143°) contained in a 2-l. round-bottomed flask is added, with shaking, 318 ml. (2.76 moles) of cold (5°) 30% hydrogen peroxide. The mixture is heated in an oil bath for 24 hours, with the internal temperature adjusted to 70 ± 5°. The excess acetic acid and water are removed under reduced pressure (30 mm.), and, after 500 ml. of distillate has been collected, the residue is diluted with 200 ml. of water and concentrated again, with the collection of 200 ml. of distillate. The residual mixture is cooled to 0–5° in an ice-salt bath, and 500 ml. of cold (0–5°) 40% aqueous sodium hydroxide solution is added slowly with shaking. The strongly alkaline solution is extracted with 2 l. of chloroform, and the extracts are given preliminary drying over anhydrous sodium carbonate. The extracts are filtered and concentrated by distillation under reduced pressure. The product is distilled under vacuum, b.p. 84–85°/0.3 mm., and the yield of 3-methylpyridine-1-oxide is 175–180 g. (73–77%).

2. Vigorous refluxing with evolution of nitrogen oxides occurs. Serious flooding of the condenser may result if no cooling is applied.

3. During the addition of sodium carbonate, large volumes of nitrogen oxides are evolved. In experiments where smaller quantities of sodium carbonate were used, lower yields (ca. 62%) were obtained.

3. Methods of Preparation

3-Methylpyridine-1-oxide has been prepared by the oxidation of 3-methylpyridine with hydrogen peroxide in glacial acetic acid,[4,5] with 40% peracetic acid and sodium acetate,[6] and with perbenzoic acid in benzene.[7]

3-Methyl-4-nitropyridine-1-oxide has been prepared by the nitration of 3-methylpyridine-1-oxide hydrochloride with a mixture of concentrated sulfuric acid and potassium nitrate.[6] The preparation of this compound has been mentioned briefly by Talikowa,[8] but no experimental details have been given.

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[1] Frick Chemical Laboratory, Princeton University, Princeton, New Jersey.

[2] Noyes Chemical Laboratory, University of Illinois, Urbana, Illinois.

[3] Mosher, Turner, and Carlsmith, *Org. Syntheses*, **33**, 79 (1953).

[4] Ochiai, Ikehara, Kato, and Ikekawa, *J. Pharm. Soc. Japan*, **71**, 1385 (1951) [*C. A.*, **46**, 7101 (1952)].

[5] Boekelheide and Linn, *J. Am. Chem. Soc.*, **76**, 1286 (1954).

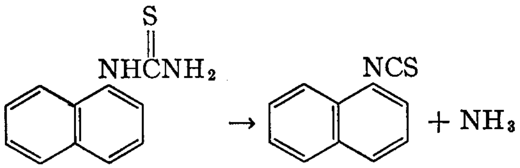
[6] Herz and Tsai, *J. Am. Chem. Soc.*, **76**, 4184 (1954).

[7] Matsumura, *J. Chem. Soc. Japan*, **74**, 446 (1953) [*C. A.*, **48**, 6442 (1954)].

[8] Talikowa, *Wiadomości Chem.*, **7**, 169 (1953) [*C. A.*, **48**, 1337 (1954)].

α-NAPHTHYL ISOTHIOCYANATE

(Isothiocyanic acid, 1-naphthyl ester)



Submitted by J. Cymerman-Craig, M. Moyle, and R. A. White.[1]
Checked by N. J. Leonard and F. H. Owens.

1. Procedure

In a 500-ml. round-bottomed flask fitted with a reflux condenser are placed 16.2 g. (0.08 mole) of dry α-naphthylthiourea (Note 1) and 180 ml. of redistilled chlorobenzene. The flask is heated at the reflux temperature by means of an electric heating mantle. Evolution of ammonia begins almost at once, and all of the solid dissolves after 30–45 minutes. The solution is maintained at reflux for 8 hours (Note 2) and then evaporated on a steam bath at water-pump pressure to remove all of the chlorobenzene. The residue crystallizes on cooling and is extracted with four 30-ml. portions of boiling hexane (Note 3). Removal of solvent from the combined hexane extracts affords pale yellow crystals of α-naphthyl isothiocyanate, m.p. 58–59°. The yield is 12.7–13.0 g. (86–88%). Recrystallization from hexane (9 ml. of hexane for 1 g. of solute) gives colorless needles, melting point unchanged (Note 4).

2. Notes

1. α-Naphthylthiourea may be prepared by the method of Frank and Smith, *Org. Syntheses*, Coll. Vol. **3**, 735 (1955), or by the method of de Clermont, *Ber.*, **9**, 446 (1876), and Bertram, *Ber.*, **25**, 48 (1892).

2. The checkers found that a 24-hour heating period increased the yield of α-naphthyl isothiocyanate to 95%.

3. A fifth extraction yields no further product. The residue insoluble in hexane was found by the submitters to consist of 1.3–1.9 g. of a mixture of equal parts of di-α-naphthylthiourea and α-naphthylthiourea, m.p. 178–181°.

4. The method is generally applicable to the preparation of aryl isothiocyanates. Using this procedure, the submitters have prepared the following isothiocyanates, with the yields and times of refluxing indicated: phenyl, 44%, 8 hours; *o*-chlorophenyl, 46, 8; *p*-bromophenyl, 73, 8; *p*-biphenylyl, 49, 6; β-naphthyl, 70, 10; 9-phenanthryl, 70, 10; 1-pyrenyl, 72, 10.

3. Methods of Preparation

Aryl isothiocyanates can be prepared by the action of thiophosgene on the arylamine[2] (this reaction fails with naphthyl compounds),[3] by fission of a *sym*-diarylthiourea with acidic reagents[4] (this reaction involves the loss of half the amine used), and by the decomposition of an ammonium aryldithiocarbamate[5] (low yields are reported for naphthyl and other compounds).[5,6] The procedure described here is that of Baxter, Cymerman-Craig, Moyle, and White.[7]

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[1] University of Sydney, Sydney, Australia.

[2] Dyson, *Org. Syntheses*, Coll. Vol. **1**, 165 (1941).

[3] Connolly and Dyson, *J. Chem. Soc.*, **1935**, 679.

[4] Werner, *J. Chem. Soc.*, **59**, 396 (1891).

[5] Dains, Brewster, and Olander, *Org. Syntheses*, Coll. Vol. **1**, 447 (1941).

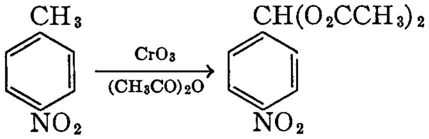
[6] Dains, Brewster, and Olander, *Univ. Kansas Sci. Bull.*, **13**, 1 (1922) [*C. A.*, **17**, 543 (1923)].

[7] Baxter, Cymerman-Craig, Moyle, and White, *Chemistry & Industry*, **1954**, 785.

o- AND *p*-NITROBENZALDIACETATE

(Toluene-α,α-diol, *o*-nitro-, diacetate)

(Toluene-α,α-diol, *p*-nitro-, diacetate)



Submitted by Tamio Nishimura.[1]
Checked by T. L. Cairns and R. E. Foster.

1. Procedure

p-Nitrobenzaldiacetate. In a 2-l., three-necked flask provided with a mechanical stirrer, dropping funnel, and thermometer, surrounded by an ice-salt bath, are placed 400 ml. of acetic anhydride (Note 1) and 50 g. (0.36 mole) of *p*-nitrotoluene (Note 2). To this solution is added slowly, with stirring, 80 ml. of concentrated sulfuric acid. When the mixture has cooled to 0°, a solution of 100 g. (1.0 mole) of chromium trioxide (Note 3) in 450 ml. of acetic anhydride is added slowly, with stirring, at such a rate that the temperature does not exceed 10° (Note 4), and stirring is continued for 2 hours at 5–10° in an ice-water bath after the addition is complete. The contents of the flask are poured into two 3-l. beakers one-third filled with chipped ice, and water is added until the total volume is 5–6 l. The solid is separated by suction filtration and washed with water until the washings are colorless. The product is suspended in 300 ml. of 2% aqueous sodium carbonate solution and stirred. After thorough mixing, the solid is collected on a filter (Note 5), washed with water and finally with 20 ml. of ethanol. The product, after drying in a vacuum desiccator, weighs 60–61 g. (66–67% of the theoretical amount), m.p. 121–124° (Note 6).

o-Nitrobenzaldiacetate. *o*-Nitrotoluene (the fraction boiling at 217–219° of commercial product) is treated in a manner exactly similar to that for *p*-isomer, except that the reaction mixture is stirred mechanically for 3 hours at 5–10° after the addition of chromium trioxide is complete. Washing of the crude product with ethanol is omitted; instead, the crude product is heated under reflux with petroleum ether for 30 minutes. The product melts at 82–84° with preliminary softening. The yield is 33.6–34.5 g. (37–38%).

2. Notes

1. The industrial grade of acetic anhydride was used without further purification.
2. Commercial *p*-nitrotoluene (m.p. 53–54°) was used.
3. The chromium trioxide was of 97% purity. Cooling is necessary on dissolving chromium trioxide in acetic anhydride. *Caution.* Addition of acetic anhydride *to* solid chromium trioxide has resulted in explosive decompositions. The trioxide should be added in small portions to the cooled anhydride.
4. With a good ice-salt bath, the time required for the addition is 1.5–2.0 hours.
5. By acidification of the sodium carbonate washings, 2–4 g. of *p*-nitrobenzoic acid, m.p. 235–237°, is obtained.
6. A similar procedure may be used for the preparation of *p*-cyanobenzaldiacetate from *p*-tolunitrile. Information submitted by Rorig and Nicholson, of G. D. Searle and Company, indicates that the critical step in this preparation is to maintain the reaction temperature below 10° throughout the process. Exposure of *p*-cyanobenzaldiacetate to excess chromic, acetic, and sulfuric acids causes a reduction in yield. During the oxidation care should be taken to prevent chromium trioxide from adhering to the walls of the flask above the reaction mixture and then dropping in large amounts into the solution.

3. Methods of Preparation

These have been reviewed in an earlier volume.[2] *p*-Nitrobenzaldehyde has also been prepared in 32% yield by heating *p*-nitrobenzyl chloride with potassium *tert*-butylperoxide.[3] The preparation of *o*-nitrobenzaldiacetate has been described in an earlier volume.[4]

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[1] Kitasato Institute for Infectious Diseases, 138, Shiba-Shirokane-Sanko-cho, Minato-ku, Tokyo, Japan.

[2] Lieberman and Connor, *Org. Syntheses*, Coll. Vol. **2**, 441 (1943).

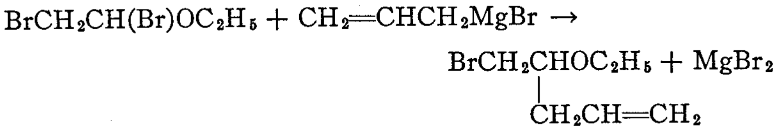
[3] Campbell and Coppinger, *J. Am. Chem. Soc.*, **73**, 1788 (1951); U. S. pat. 2,628,256 [*C. A.*, **48**, 724 (1954)].

[4] Tsang, Wood, and Johnson, *Org. Syntheses*, Coll. Vol. **3**, 641 (1955).

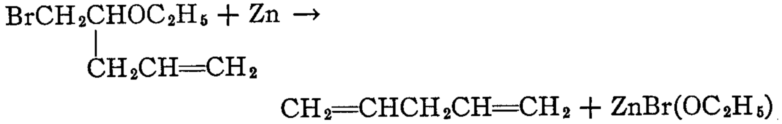
1,4-PENTADIENE

$$CH_3CHO + C_2H_5OH + HCl \rightarrow CH_3CH(Cl)OC_2H_5 + H_2O$$

$$CH_3CH(Cl)OC_2H_5 + Br_2 \rightarrow BrCH_2CH(Br)OC_2H_5 + HCl$$



$$BrCH_2CH(Br)OC_2H_5 + CH_2{=}CHCH_2MgBr \rightarrow \underset{\displaystyle |\atop \displaystyle CH_2CH{=}CH_2}{BrCH_2CHOC_2H_5} + MgBr_2$$



$$\underset{\displaystyle |\atop \displaystyle CH_2CH{=}CH_2}{BrCH_2CHOC_2H_5} + Zn \rightarrow CH_2{=}CHCH_2CH{=}CH_2 + ZnBr(OC_2H_5)$$

Submitted by Oliver Grummitt, E. P. Budewitz, and C. C. Chudd.[1]
Checked by William S. Johnson, E. Saito, and Donald J. Reif.

1. Procedure

A. *α-Chloroethyl ethyl ether.* A mixture of 200 g. (201 ml.) of redistilled paraldehyde, b.p. 121–122.5° (equivalent to 4.54 moles of acetaldehyde), and 200 g. (254 ml., 4.34 moles) of absolute ethanol is placed in a 1-l. three-necked flask fitted with a mechanical stirrer and a gas inlet tube reaching to the bottom of the flask. The mixture is cooled to −5° in a mixture of Dry Ice and acetone, and dry hydrogen chloride (Note 1) is passed into the stirred reaction mixture maintained at about −5° until 200 g. (5.48 moles) has been absorbed. During this operation, which requires about 2 hours, the reaction mixture separates into two layers. The upper layer of crude α-chloroethyl ethyl ether is removed, and the dissolved hydrogen chloride is swept out by bubbling dry nitrogen gas through the mixture. The product is dried overnight with 25–50 g. of anhydrous calcium sulfate (Note 2). The yield of crude α-chloroethyl ethyl ether (Note 3) is 411–432 g. (87–92% based on ethanol). The product is not distilled, since it decomposes readily.

B. *α,β-Dibromoethyl ethyl ether.* Four hundred and twenty-five grams (3.92 moles) of the crude α-chloroethyl ethyl ether (part A) is placed in a dry 1-l. three-necked flask, fitted with a dropping funnel, mechanical stirrer, and an outlet tube leading to a gas absorption trap [2] to dispose of the hydrogen chloride evolved. The flask is cooled in an ice bath, and 625 g. (200 ml., 3.92 moles) of bromine is added in small portions from the dropping funnel with stirring. The reaction mixture is allowed to become almost colorless after each addition. When all of the bromine has been added (5–6 hours), a slow current of dry nitrogen is bubbled through the reaction mixture to sweep out the hydrogen chloride (Note 4). The product is dried overnight with 25–50 g. of anhydrous calcium sulfate and then distilled at reduced pressure (Note 5). The yield of colorless α,β-dibromoethyl ethyl ether is 599–663 g. (66–73% based on the α-chloroethyl ethyl ether), b.p. 70–75°/27 mm., n_D^{20} 1.5097–1.5102.

C. *Allylmagnesium bromide* (Note 6). In a dry 5-l. three-necked flask, equipped with a sealed stirrer, a reflux condenser and drying tube, a pressure-equalized dropping funnel, and a nitrogen inlet tube, are placed 195 g. (8.0 gram atoms) of dry magnesium turnings and 2.4 l. of anhydrous ether. The flask is cooled in an ice bath, a small crystal of iodine is added, and a solution of 400 g. (287 ml., 3.31 moles) of allyl bromide (redistilled, b.p. 69–71°) in an equal volume of anhydrous ether is added dropwise over a period of 17 hours. During the reaction a slow stream of dry, oxygen-free nitrogen is passed through the flask. After the addition is complete, the reaction mixture is stirred for 30 minutes. The Grignard reagent is decanted into a dry, graduated storage bottle; the residue in the flask is washed with 150–200 ml. of dry ether; and the wash liquid is added to the storage bottle. Samples of the clear supernatant solution are analyzed by acidimetric titration.[3] The yield of allylmagnesium bromide is 2.62–2.95 moles (79–89%).

D. *α-Allyl-β-bromoethyl ethyl ether.* The same apparatus is used as in the preparation of allylmagnesium bromide. The flask is charged with an amount of the Grignard solution (part C) equivalent to 2.78 moles of allylmagnesium bromide (or chloride) and cooled in an ice bath. A solution of 580 g. (2.5 moles) of α,β-dibromoethyl ethyl ether (part B) in an equal volume of anhydrous ether is added slowly with stirring over a period of 3–4 hours. The mixture is allowed to stand overnight and is then hydrolyzed with 75 ml. of 20% acetic acid followed by 500 ml. of water. The ether layer is separated, washed with four 100-ml. portions of 10% aqueous sodium bicarbonate solution followed by four 100-ml. portions of saturated aqueous sodium chloride solution, dried over 100 g. of anhydrous calcium sulfate, and distilled under reduced pressure. The yield of colorless α-allyl-β-bromoethyl ethyl ether is 370–396 g. (77–82% based on the α,β-dibromoethyl ethyl ether), b.p. 72–75°/21 mm., n_D^{20} 1.4600–1.4606.

E. *1,4-Pentadiene.* A 2-l. three-necked flask is equipped with a sealed stirrer and a 28-cm. reflux condenser, at the top of which is a 2.5 × 35 cm. Vigreux fractionating column attached to an efficient condenser arranged for distillation. Water at 35–40° is pumped through the reflux condenser, ice water is pumped through the downward condenser, and the receiver is ice-cooled and attached to a trap cooled by Dry Ice. The flask is charged with 380 g. (1.97 moles) of α-allyl-β-bromoethyl ethyl ether (part D) in 550 ml. of *n*-butyl alcohol; then 550 g. (8.4 gram atoms) of zinc dust and 2 g. of anhydrous zinc chloride are added. The mixture is stirred vigorously and heated gradually to the point where the pentadiene distils at a rate of about one drop every 2 seconds. The reflux condenser and column return most of the butyl alcohol to the flask. The reaction takes 5–6 hours for completion. The distillate is washed with five 100-ml. portions of ice water to remove most of the butyl alcohol and is then dried overnight with 15 g. of calcium chloride. The crude dry product is distilled through a 2.5 × 35 cm. Vigreux column to give 97–102 g. (72–76%) of colorless 1,4-pentadiene, b.p. 26–27°/740 mm., n_D^{20} 1.3887–1.3890.

2. Notes

1. Commercial hydrogen chloride from a cylinder is dried by passage through a train consisting of a wash bottle of concentrated sulfuric acid, a 25-cm. calcium chloride tube, and finally an empty safety trap.

2. This ether is a lachrymator, hydrolyzes rapidly in the presence of moisture, and resinifies readily at temperatures above 0°. It is advisable to store it in a Dry Ice chest during drying and until the next step is to be run. Hydrolysis at low temperatures appears to be negligible.

3. Analysis of the crude material for chlorine gave 31.74% (calcd. 32.69%).

4. It is necessary to remove the hydrogen chloride because it promotes decomposition of the dibromoether.

5. Distillation is required to remove aldehyde, alcohol, and water which would react with the Grignard reagent in the next step. α,β-Dibromoethyl ethyl ether is also a lachrymator.

6. Either allylmagnesium bromide or allylmagnesium chloride may be used. The former is more conveniently prepared in higher yield and in a more concentrated solution, but allyl chloride is considerably less expensive than allyl bromide. The submitters state that the chloride is prepared just as the bromide with the following exceptions: the temperature is maintained between −10 and −15° with a Dry Ice-acetone cooling bath; 76.5 g. (82 ml., 1 mole) of allyl chloride (b.p. 45–47°) dissolved in an equal volume of dry ether is used (the amounts of all other reagents are unaltered); the addition is carried out over a 12-hour period, then the cooling bath is removed, and the mixture (containing considerable solid) is stirred until it reaches room temperature, during which time most of the solid material dissolves. The yield of allylmagnesium chloride as determined by acidimetric titration [3] is 0.67–0.69 mole (67–69%).

3. Methods of Preparation

1,4-Pentadiene has been prepared by the interaction of allyl bromide and vinyl bromide in the presence of magnesium[4] and by the pyrolysis of 1,5-pentanediol diacetate[5,6] or 4-penten-1-ol acetate.[6,7] The present procedure is essentially that of Shoemaker and Boord[8] with some modifications.[9]

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[1] Western Reserve University, Cleveland, Ohio.

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

[3] Gilman, Zoellner, and Dickey, *J. Am. Chem. Soc.*, **51**, 1577 (1929).

[4] Kogerman, *J. Am. Chem. Soc.*, **52**, 5060 (1930).

[5] Schniepp and Geller, *J. Am. Chem. Soc.*, **67**, 54 (1945).

[6] Paul and Tchelitcheff, *Bull. soc. chim. France*, [5], **15**, 110 (1948).

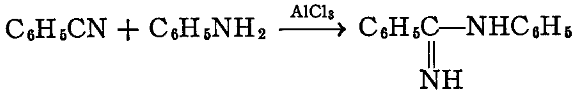
[7] Paul and Normant, *Bull. soc. chim. France*, [5], **11**, 367 (1944).

[8] Shoemaker and Boord, *J. Am. Chem. Soc.*, **53**, 1505 (1931).

[9] Kistiakowsky, Ruhoff, Smith, and Vaughan, *J. Am. Chem. Soc.*, **58**, 146 (1936); Elsner and Wallsgrove, *J. Inst. Petroleum*, **35**, 259 (1949).

N-PHENYLBENZAMIDINE

(Benzamidine, N-phenyl-)



$$C_6H_5CN + C_6H_5NH_2 \xrightarrow{AlCl_3} C_6H_5\underset{\underset{NH}{\|}}{C}{-}NHC_6H_5$$

Submitted by F. C. Cooper and M. W. Partridge.[1]
Checked by T. L. Cairns, R. E. Benson, and V. J. Webers.

1. Procedure

Sixty-two grams (61 ml., 0.67 mole) of aniline (Note 1) is mixed with 68.5 g. (0.66 mole) of benzonitrile in a 250-ml., wide-mouthed flask, and, during about 20 minutes, 89 g. (0.67 mole, calculated as $AlCl_3$) of a freshly opened sample of powdered, anhydrous aluminum chloride is added in portions with thorough stirring (Note 2). The mixture is then heated at 200° for 30 minutes (Note 3), and, while still molten, is poured slowly into a thoroughly stirred mixture of 20 ml. of concentrated hydrochloric acid and 1.6 l. of water. After the addition of 20 g. of activated carbon, the suspension is stirred while being externally cooled in running water and is then filtered through a kieselguhr filter (Note 4). The filtrate is poured in a steady stream into a stirred solution of 220 g. of sodium hydroxide in 1.2 l. of water. The flocculent precipitate is collected on alkali-resistant paper in a 12-cm. Büchner funnel with the aid of suction, washed with water (Note 5), broken up thoroughly, and air-dried at room temperature to constant weight. The yield of white product, m.p. 111–115°, is 90–96 g. (69–74%). This material is sufficiently pure for most purposes. Recrystallization from benzene (60 ml. per 10 g. of amidine) yields 56–74 g. of white powder; concentration of the mother liquors raises the total yield of N-phenylbenzamidine to 69–86 g. (53–66%), melting at 114–115.5°.

2. Notes

1. It is preferable to use aniline freshly redistilled from a small quantity of zinc dust.
2. The reaction is strongly exothermic. Although loss of reagents by volatilization is small, it is advisable to close the flask with a loose plug of cotton wool.
3. Below about 180° the mixture is too stiff to be stirred, but at 200° it is a mobile liquid.
4. A suitable filter is prepared by distributing a slurry of 10–15 g. of "Super-Cel" in water on a filter paper in a 12-cm. Büchner funnel and washing with water with the aid of suction until a clear filtrate is obtained.
5. Washing is best effected by vigorously stirring the cake with water until it is completely dispersed, collecting again, and draining well; three such washings are usually sufficient.

3. Methods of Preparation

This method is based on the procedure of Oxley, Partridge, and Short.[2] N-Phenylbenzamidine has also been prepared by heating aniline hydrochloride with benzonitrile or thiobenzamide[3] or by heating aniline benzenesulfonate with benzonitrile,[4] by the action of sodium on a mixture of aniline and benzonitrile,[5] by treating phenylcyanamide with phenylmagnesium bromide,[6] by the interaction of aniline and benziminoethyl ether hydrochloride,[7] by the reaction between N-phenylbenzimidyl chloride and ammonia,[8] by the action of sodamide on benzylidene aniline,[7,9] by hydrogenating benzanilide oxime,[10] and by treating benzophenone oxime benzenesulfonate with ammonia.[11]

[1] Department of Chemistry, The University, Nottingham, England.

[2] Oxley, Partridge, and Short, *J. Chem. Soc.*, **1947**, 1112; Short and Partridge (Boots Pure Drug Company), Brit. pat. 598,453 [*C. A.*, **42**, 6854 (1948)]; U. S. pat. 2,450,386 [*C. A.*, **43**, 3456 (1949)].

[3] Bernthsen, *Ann.*, **184**, 348 (1877).

[4] Oxley and Short, *J. Chem. Soc.*, **1946**, 147.

[5] Lottermoser, *J. prakt. Chem.*, **54**, 116 (1896).

[6] Busch and Hobein, *Ber.*, **40**, 4298 (1907).

[7] Lossen and Kobbert, *Ann.*, **265**, 138 (1891).

[8] Ghadiali and Shah, *J. Univ. Bombay*, **6**, 127 (1937) [*C. A.*, **32**, 3761 (1938)].

[9] Kirssanow and Iwastchenko, *Bull. soc. chim. France*, [5], **2**, 2118 (1935).

[10] Barber and Self (May and Baker Ltd.), U. S. pat. 2,375,611 [*C. A.*, **39**, 3544 (1945)].

[11] Oxley and Short, *J. Chem. Soc.*, **1948**, 1519.

PROPIOLALDEHYDE

(Propynal)

$$HC{\equiv}C{-}CH_2OH \xrightarrow{CrO_3} HC{\equiv}C{-}CHO$$

Submitted by J. C. Sauer.[1]
Checked by John C. Sheehan and E. R. Gilmont.

1. Procedure

Caution! Propiolaldehyde is lachrymatory.

A 3-l. three-necked round-bottomed flask is fitted with a thermometer, a graduated dropping funnel (Note 1), a stirrer (Note 2), a fine capillary tube for introducing nitrogen near the bottom of the flask, and an exit tube attached through a manometer to three traps set up in series. In the flask are placed 360 ml. of 33% (by volume) propargyl alcohol [112.1 g. (120 ml., 2.0 moles)] (Note 3) and a cooled solution of 135 ml. of sulfuric acid and 200 ml. of water. The flask is cooled in an ice-salt mixture. While the contents of the flask are cooling, the first trap is cooled to about −15° with acetone and Dry Ice. The last two traps in the series are cooled to −78° with acetone and Dry Ice (Note 4). The pressure in the system is reduced to 40–60 mm., nitrogen is introduced through the capillary, and the mixture is stirred vigorously. A solution of 210 g. of commercial chromium trioxide (2.1 moles) in 400 ml. of water and 135 ml. of sulfuric acid is added dropwise in the course of about 3 hours while maintaining a reaction temperature of 2–10°. After the addition of the chromium trioxide, the ice bath is removed, and the flask is permitted to warm to room temperature while the pressure is gradually lowered to 14–20 mm. to remove the last of the aldehyde. The condensates of the three traps are combined (Note 5) and dried over anhydrous magnesium sulfate. The propiolaldehyde is distilled through a 16-in. column packed with platinum gauze. The fraction distilling at 54–57° weighs 38–44 g. (35–41%), n_D^{25} 1.4050 (Notes 6 and 7).

2. Notes

1. The end of the dropping funnel extends about 2 in. into the flask from the opening and is drawn into a capillary. This is done to ensure the introduction of the chromic acid solution in the form of small droplets.

2. A "Trubore" stirring system with a 29/26 joint was used for stirring under vacuum.

3. Propargyl alcohol is available from the General Aniline and Film Corporation, Easton, Pennsylvania.

4. If the cooling bath for the first trap is lowered much below −15°, plugging of the trap is likely to occur. These traps are connected so that the vapor enters the larger, annular space, impinging on the cold wall before entering (and possibly plugging) the smaller inner tube.

5. The material in the first trap contains a considerable amount of water. In order to facilitate separation, the checkers saturated this mixture with sodium chloride. The upper layer, consisting of nearly pure propiolaldehyde, was combined with the contents of the second and third traps and dried over 5 g. of anhydrous magnesium sulfate. Distillation through a 12-in. vacuum-jacketed Vigreux column gave directly propiolaldehyde comparable in yield and quality with the final product described by the submitter in Note 6.

6. Considerable water is carried into the traps, and the distillate contains 3–10% water. The last of the water can be removed by drying the distillate a second time over magnesium sulfate and redistilling. In this way there is obtained 30–37 g. (28–34%) of propiolaldehyde distilling at 55–56°, n_D^{25} 1.4032–1.4034.

7. The material should be stored in glass-stoppered bottles, since contaminants from rubber stoppers may be sufficient to catalyze decomposition. A sample of propiolaldehyde underwent no noticeable change after four months' storage in a Dry Ice chest. However, this aldehyde undergoes extremely vigorous polymerization or decomposition in the presence of alkalies. For example, propiolaldehyde undergoes a change with almost explosive force in the presence of pyridine. Accordingly, *exceptional care should be used in the handling of propiolaldehyde.*

3. Methods of Preparation

The procedure described is that of Wille and Saffer.[2] Propiolaldehyde has also been prepared by the oxidation of propargyl alcohol using ammonium dichromate[3] or manganese dioxide in 10% sulfuric acid.[4] Propiolaldehyde has also been prepared by warming the dimethyl or diethyl acetal with dilute sulfuric acid.[5]

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[1] Contribution No. 364 from the Chemical Department, Experimental Station, E. I. duPont de Nemours and Company, Wilmington, Delaware.

[2] Wille and Saffer, *Ann.*, **568**, 40 (1950).

[3] Quilico and Palazzo, *Proc. XI Intern. Congr. Pure and Applied Chem.*, **2**, 253 (1947) [*C. A.*, **45**, 7107 (1951)].

[4] Copenhaver and Bigelow, *Acetylene and Carbon Monoxide Chemistry*, p. 124, Reinhold Publishing Corporation, New York 18, N. Y., 1949.

[5] Claisen, *Ber.*, **31**, 1022 (1898).

PUTRESCINE DIHYDROCHLORIDE

$$\mathrm{(CH_2)_4(CO_2C_2H_5)_2} \xrightarrow{\mathrm{N_2H_4}} \mathrm{(CH_2)_4(CONHNH_2)_2} \xrightarrow{\mathrm{HNO_2}} \mathrm{(CH_2)_4(CON_3)_2}$$

$$\mathrm{(CH_2)_4(CON_3)_2} \longrightarrow \mathrm{(CH_2)_4(NCO)_2} + \mathrm{2N_2}$$

$$\mathrm{(CH_2)_4(NCO)_2} \xrightarrow[\mathrm{H_2O}]{\mathrm{HCl}} \mathrm{(CH_2)_4(NH_2 \cdot HCl)_2}$$

Submitted by PETER A. S. SMITH.[1]
Checked by JAMES CASON and WM. DEACETIS.

1. Procedure

A. *Adipyl hydrazide.* A solution of 120 ml. of 85% aqueous hydrazine hydrate (105 g., 2.0 moles) (Note 1) and 25 ml. of absolute ethanol is brought to a gentle boil in a 500-ml. three-necked flask provided by means of ground glass joints with a ball joint-sealed mechanical stirrer (Note 2), a reflux condenser, and a dropping funnel. One hundred and one grams (0.5 mole) of diethyl adipate[2] is added dropwise to the boiling stirred solution at such a rate that a separate liquid phase does not accumulate in the reaction mixture (Note 3). This operation requires 1–2 hours, at the end of which time the contents of the flask will have largely crystallized. The boiling is continued for 5 minutes after the completion of the addition, and the contents of the flask are then cooled to room temperature with running water. The crystals are washed onto a Büchner funnel with the aid of about 100 ml. of absolute ethanol used in several portions. The precipitate is dried by suction, and the product is washed once with 25 ml. of ether. After drying in air (or at 100°) the adipyl hydrazide weighs 77–80 g. (88–92%) and is of good quality, with a melting point above 170° (Note 4). Concentration of the filtrate to a volume of about 25 ml. in an air stream on a steam bath yields an additional 2.5 g. of nearly pure material; total yield 91–95%.

B. *Putrescine dihydrochloride.* A 2-l. wide-mouthed Erlenmeyer flask containing 200 ml. of concentrated hydrochloric acid and 400 g. of cracked ice is clamped in an ice-salt bath and provided with an efficient stirrer (inefficient stirring may lower the yield). The stirring is started, and 80 g. (0.46 mole) of adipyl hydrazide is added all at once, followed by 500 ml. of ether (Note 5). While the temperature is maintained below 10° (Note 6), a solution of 80 g. (1.15 moles) of sodium nitrite in 150 ml. of water is added over about 30 minutes through a dropping funnel whose stem reaches below the bottom of the ether layer, but not into the path of the stirrer. *The operations in the next paragraph should be conducted without delay after the completion of the addition of the nitrite.*

The cold reaction mixture, which may be freed from suspended solid by rapid filtration through a cotton plug, is transferred to a 2-l. or 3-l. separatory funnel, and the aqueous layer is drawn off into the original reaction flask. The ether layer is poured into a 2-l. Erlenmeyer flask containing about 50 g. of anhydrous calcium chloride, and this flask is placed in the ice bath in which the diazotization was run. The cold aqueous layer is then extracted with two 100-ml. portions of chilled ether, which are combined with the first ether extract. After 5 minutes with occasional swirling, the ether solution of adipyl azide (Note 7) is sufficiently dry, and it is poured into a 2-l. round-bottomed flask containing 350–400 ml. of benzene (Note 8). The calcium chloride is rinsed with a 50-ml. portion of ether, which is added to the same flask.

The ether is distilled gently from a steam bath, preferably through a short fractionating column; nitrogen will be evolved at the same time. When the volume of the contents of the flask has reached about 400 ml., the flask is heated strongly on the steam bath for about 15 minutes to complete the decomposition of the azide (Note 9). The flask is removed from the steam bath, and 200 ml. of concentrated hydrochloric acid is added cautiously to the hot solution (Note 10). The flask is allowed to stand with occasional swirling until the carbon dioxide evolution has ceased (about 15 minutes). The mixture is heated strongly on a steam bath for about 15 minutes more, and the solvents are then distilled from a steam bath under aspirator vacuum (Note 11). When the contents of the flask have become a crystalline paste, the vacuum is temporarily disconnected, and the inner walls of the flask are washed down with about 50 ml. of ethanol. The vacuum is renewed cautiously, and the mixture is distilled to dryness (Note 12).

The residue of crystalline putrescine dihydrochloride is rinsed onto a Büchner funnel with the aid of 100–200 ml. of absolute ethanol used in several portions. The last portions of ethanol are used as wash liquid for the crystals. The crystals are finally pressed dry and washed with 25 ml. of ether. The air-dried product weighs 53–55 g. (72–74%) and melts above 275°. Analysis for chlorine indicates that the salt is anhydrous. Concentration of the filtrate to a volume of about 25 ml. yields an additional 1–2 g.; total yield 73–77%. The entire synthesis may be completed in one day.

2. Notes

1. Eastman Kodak Company practical grade was used.

2. Mechanical stirring is not strictly necessary; however, severe bumping is sometimes encountered if it is not used. Hydrazine attacks both cork and rubber. If a dropping funnel with ground glass joint is not available, an ordinary dropping funnel may be placed at the top of the reflux condenser.

3. If unreacted ester is allowed to accumulate, some secondary hydrazide may be formed, with consequent loss of yield in the next step.

4. The melting point of adipyl hydrazide reported in the literature [4] is 171°; however, values as high as 179° have been observed. The checkers observed values of 174–177° and 179–181° for products of two runs, when the crystals were placed on a hot stage after the temperature had reached 160°.

5. Ethanol-free ether should be used. Dropwise addition of 50 ml. of concentrated sulfuric acid to 1 l. of ether, and distillation of the ether from a steam bath gives a satisfactory solvent.

6. To maintain this temperature at the rate of addition of the nitrite indicated will probably require the occasional addition of cracked ice to the reaction mixture. Only occasional checking of the temperature is necessary. If the temperature is kept below 0°, slightly better yields are obtained. The addition of Dry Ice directly to the ether layer accomplishes this easily. Temperatures above 10° cause a loss in yield, but apparently create no hazard.

7. Ethereal solutions of adipyl azide are quite safe, but the free azide is somewhat explosive and should not be isolated. If storage of an intermediate is desired, the azide should be converted to the urethane by the procedure given below. The urethane is quite stable to storage; also, the procedure *via* the urethane gives improved yields in some amine syntheses.

The dried ethereal solution of adipyl azide is added to a 2-l. flask containing 400 ml. of absolute ethanol, and the ether and some of the ethanol are distilled on a steam bath through a short fractionating column. When the volume has reached about 200 ml., the solution may be poured into a 500-ml. Erlenmeyer flask, and the remainder of the solvents removed on a steam bath by means of an air stream. The residual, waxy, crystalline cake of N,N′-dicarbethoxyputrescine weighs 84–91 g. (79–85%) and melts at 76–81°. It may be kept indefinitely.

If the urethane is to be hydrolyzed immediately, there is no need to isolate it. Instead, after distillation of most of the ether and alcohol from the flask in which the urethane is formed, 700 ml. of concentrated hydrochloric acid is added, and the mixture is heated under reflux for 4 hours. The solution is then distilled from a steam bath under aspirator vacuum (Note 11), and the putrescine dihydrochloride is isolated as described above. The total yield is 55–57 g. (74–77%).

The isolated urethane may be hydrolyzed by this procedure at any time. For the hydrolysis step, the yield is 89–91%.

8. Commercial benzene may be used.

9. The rearrangement of the azide is complete when nitrogen evolution ceases. This is usually concluded in the time indicated, but occasionally takes longer.

10. Carbon dioxide is evolved copiously at this point and may cause the solution to foam over if the acid is not added cautiously.

11. Alternatively, the solution may be poured into a 1-l. flask for this operation.

12. Solid putrescine dihydrochloride should not be heated unduly long at 100°, as it may turn pink.

3. Methods of Preparation

Putrescine dihydrochloride has been prepared by the Hofmann degradation of adipamide;[3,4,5] by the Curtius degradation of adipyl hydrazide through the urethane;[6] by the Curtius degradation of adipyl azide obtained from adipyl chloride and sodium azide;[7] by the Schmidt degradation of adipic acid with hydrogen azide;[8] by the reduction of succinonitrile,[9] succinaldoxime,[10,11] or γ-phthalimidobutyronitrile[12,13] with sodium; and from N-benzoyl-γ-iodobutylamine.[14]

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[1] University of Michigan, Ann Arbor, Michigan.

[2] Mićović, *Org. Syntheses*, Coll. Vol. **2**, 264 (1943).

[3] Farbenfabriken F. Bayer and Company, Ger. pat. 232,072 [*Friedlaender*, **10**, 106 (1910–1912)].

[4] von Braun and Lemke, *Ber.*, **55B**, 3529 (1922).

[5] Vogel, *J. Chem. Soc.*, **1929**, 1489.

[6] Curtius and Darmstaedter, *J. prakt. Chem.*, **91**, 11 (1915).

[7] Naegeli and Lendorff, *Helv. Chim. Acta*, **15**, 49 (1932).

[8] von Braun and Pinkernelle, *Ber.*, **67B**, 1059 (1934).

[9] Ladenburg, *Ber.*, **19**, 780 (1886).

[10] Ciamician and Zanetti, *Ber.*, **22**, 1970 (1889).

[11] Willstätter and Heubner, *Ber.*, **40**, 3871 (1907).

[12] Kanevskaya, *Zhur. Russ. Fiz. Khim. Obshchestva*, **59**, 646 (1927) [*Chem. Zentr.*, **1928**, I, 1026].

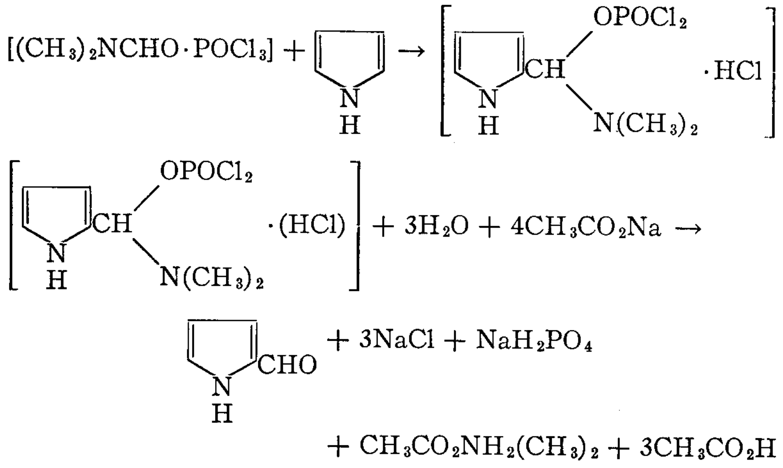
[13] Keil, *Ber.*, **59B**, 2816 (1926).

[14] Dudley and Thorpe, *Biochem. J.*, **19**, 845 (1925).

2-PYRROLEALDEHYDE

(2-Pyrrolecarboxaldehyde)

$$(CH_3)_2NCHO + POCl_3 \rightarrow [(CH_3)_2NCHO\cdot POCl_3]$$



Submitted by Robert M. Silverstein, Edward E. Ryskiewicz, and Constance Willard.[1]
Checked by Max Tishler and George Purdue.

1. Procedure

In a 3-l. three-necked round-bottomed flask, fitted with a sealed stirrer, a dropping funnel, and a reflux condenser, is placed 80 g. (1.1 moles) of dimethylformamide (Note 1). The flask is immersed in an ice bath, and the internal temperature is maintained at 10–20°, while 169 g. (1.1 moles) of phosphorus oxychloride is added through the dropping funnel over a period of 15 minutes. An exothermic reaction occurs with the formation of the phosphorus oxychloride-dimethylformamide complex. The ice bath is removed, and the mixture is stirred for 15 minutes (Note 2).

The ice bath is replaced, and 250 ml. of ethylene dichloride is added to the mixture. When the internal temperature has been lowered to 5°, a solution of 67 g. (1.0 mole) of freshly distilled pyrrole in 250 ml. of ethylene dichloride is added through a clean dropping funnel to the stirred, cooled mixture over a period of 1 hour. After the addition is complete, the ice bath is replaced with a heating mantle, and the mixture is stirred at the reflux temperature for 15 minutes, during which time there is copious evolution of hydrogen chloride.

The mixture is then cooled to 25–30°, and to it is added through the dropping funnel a solution of 750 g. (5.5 moles) of sodium acetate trihydrate (Note 3) in about 1 l. of water, cautiously at first, then as rapidly as possible. The reaction mixture is again refluxed for 15 minutes, vigorous stirring being maintained all the while (Note 4).

The cooled mixture is transferred to a 3-l. separatory funnel, and the ethylene dichloride layer is removed. The aqueous phase is extracted three times with a total of about 500 ml. of ether. The ether and ethylene chloride solutions are combined and washed with three 100-ml. portions of saturated aqueous sodium carbonate solution, which is added cautiously at first to avoid too rapid evolution of carbon dioxide. The non-aqueous solution is then dried over anhydrous sodium carbonate, the solvents are distilled, and the remaining liquid is transferred to a Claisen flask and distilled from an oil bath under reduced pressure (Note 5). The aldehyde boils at 78° at 2 mm.; there is very little fore-run and very little residue. The yield of crude 2-pyrrolealdehyde is 85–90 g. (89–95%), as an almost water-white liquid which soon crystallizes. A sample dried on a clay plate melts at 35–40°. The crude product is purified by dissolving in boiling petroleum ether (b.p. 40–60°), in the ratio of 1 g. of crude 2-pyrrolealdehyde to 25 ml. of solvent, and cooling the solution slowly to room temperature, followed by refrigeration for a few hours. The pure aldehyde is obtained from the crude in approximately 85% recovery. The over-all yield from pyrrole is 78–79% of pure 2-pyrrolealdehyde, m.p. 44–45°.

2. Notes

1. The dimethylformamide is available as technical grade DMF from the Grasselli Chemicals Department of E. I. duPont de Nemours and Company, Wilmington, Delaware.

2. If the ice bath is not removed, the mixture may solidify and must be dissolved by adding solvent and heating slightly. Mixing of the reactants at ice-bath temperature prevents discoloration. Practical grades of materials were used.

3. The use of sufficient sodium acetate is essential. If the acidic reaction products are not neutralized, the yield drops to as low as 15–20% of badly discolored product which cannot be readily purified.

4. Efficient stirring must be maintained to keep the two phases in close contact. Hydrolysis is not complete if the mixture is not heated.

5. The use of a wide-bore condenser and a simple receiver, without a stopcock, is preferable. Usually the product does not solidify at once, but occasionally it crystallizes during distillation. The use of a fraction cutter is not necessary or advisable.

3. Methods of Preparation

2-Pyrrolealdehyde has been prepared from pyrrole, chloroform, and potassium hydroxide;[2] from pyrrolemagnesium iodide and ethyl, propyl, or isoamyl formate;[3] and, by the method here described, from pyrrole, phosphorus oxychloride, and dimethylformamide.[4] Smith [4] has suggested a possible intermediate in this process. The method has also been applied to substituted pyrroles [5] and is similar to that described in this series for the preparation of *p*-dimethylaminobenzaldehyde from dimethylaniline.[6]

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[1] Stanford Research Institute, Stanford, California.

[2] Bamberger and Djerdjian, *Ber.*, **33**, 536 (1900); Fischer, Beller, and Stern, *Ber.*, **61B**, 1074 (1928).

[3] Tschelinzeff and Terentjeff, *Ber.*, **47**, 2653 (1914); Putochin, *Zhur. Russ. Fiz. Khim. Obshchestva*, **59**, 809 (1927); Putochin, *Ber.*, **59B**, 1993 (1926).

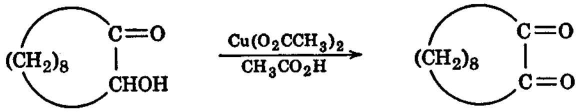
[4] Silverstein, Ryskiewicz, and Chaikin, *J. Am. Chem. Soc.*, **76**, 4485 (1954); Smith, *J. Chem. Soc.*, **1954**, 3842.

[5] Ryskiewicz and Silverstein, *J. Am. Chem. Soc.*, **76**, 5802 (1954); Chu and Chu, *J. Org. Chem.*, **19**, 266 (1954).

[6] Campaigne and Archer, *Org. Syntheses*, **33**, 27 (1953).

SEBACIL

(1,2-Cyclodecanedione)



Submitted by A. T. Blomquist and Albert Goldstein.[1]
Checked by N. J. Leonard and J. C. Little.

1. Procedure

Fifty-one grams (0.30 mole) of sebacoin (Note 1), 25 ml. of methanol, 120 g. of cupric acetate monohydrate (0.60 mole), and 300 ml. of 50% aqueous acetic acid are mixed in a 1-l. flask equipped with an efficient mechanical stirrer and a reflux condenser. The mixture is heated over a free flame until refluxing occurs. The color of the mixture changes from blue to red at approximately 75°. Refluxing is continued for 1 minute. The mixture is then allowed to cool, with stirring, to about 40° (Note 2). The mixture is filtered through filter aid ("Celite") on a sintered glass funnel to remove cuprous oxide, and the filtrate is transferred to a 2-l. separatory funnel (Note 3). Saturated aqueous sodium chloride solution (310 ml.) is added to the filtrate, which is then extracted with three 150-ml. portions of ether. The combined ether extracts are washed with three 250-ml. portions of saturated salt solution, four 250-ml. portions of 5% sodium bicarbonate solution (Foaming!), and once again with 250 ml. of saturated salt solution. The ether solution is then dried over 20 g. of anhydrous sodium or magnesium sulfate. The ether is removed by distillation at atmospheric pressure, and the residue is transferred to a 100-ml. flask and distilled under vacuum. The yield of sebacil is 44.4–45.1 g. (88–89%), b.p. 104–106°/10 mm. (Note 4).

2. Notes

1. The sebacoin-sebacil mixture obtained from the sebacoin preparation described in *Org. Syntheses*, **36**, 79 (1956), was used.
2. The sebacil may tend to crystallize during filtration if the reaction mixture is too cool.
3. The "Celite"-cuprous oxide mixture is extracted with three 50-ml. portions of ether, and the combined extracts are used as the first ether portion for the extraction of the sebacil-containing aqueous solution.
4. 1,2-Cyclononanedione has been prepared from 2-hydroxycyclononanone in 67–72% yield by this procedure.[2]

3. Methods of Preparation

1,2-Cyclodecanedione has also been prepared by oxidation of sebacoin with chromium trioxide in acetic acid.[3,4] Cupric acetate in acetic acid has been used for oxidation of an α-hydroxyketone by Ruggli and Zeller.[5]

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[1] Cornell University, Ithaca, New York.

[2] Blomquist, Liu, and Bohrer, *J. Am. Chem. Soc.*, **74**, 3643 (1952).

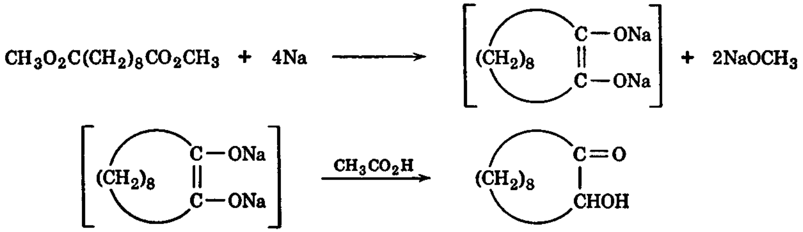
[3] Blomquist, Burge, and Sucsy, *J. Am. Chem. Soc.*, **74**, 3636 (1952).

[4] Prelog, Schenker, and Günthard, *Helv. Chim. Acta*, **35**, 1610 (1952).

[5] Ruggli and Zeller, *Helv. Chim. Acta*, **28**, 741 (1945).

SEBACOIN

(Cyclodecanone, 2-hydroxy-)



Submitted by Norman L. Allinger.[1]
Checked by N. J. Leonard, J. C. Little, and F. H. Owens.

1. Procedure

The apparatus[2] consists of a 3-l. three-necked round-bottomed creased flask, with standard ball joints and an indented cone-shaped bottom (Note 1), which is heated by means of an electric mantle and is equipped with a high-speed stirrer of stainless steel driven by a 10,000 r.p.m. motor (Note 2). One side neck is fitted with a bulb-type air-cooled condenser (Note 3), on top of which fits a 1-l. pressure-equalizing Hershberg dropping funnel (Note 4). The top of the dropping funnel is to be connected in turn to a U-tube containing a 1-cm. head of mercury. The entire apparatus is securely fastened to a sturdy support.

In the flask is placed 900 ml. of pure xylene (Note 5), and a slow stream of purified nitrogen (Note 6) is passed through the system from which the dropping funnel has been temporarily removed. The stirrer is run at slow speed, and the solvent is brought to a gentle reflux. The air stream cooling the condenser is shut off, the mercury valve is disconnected from the condenser, and a few milliliters of solvent is allowed to distil out the top of the condenser (Note 7). The dropping funnel (Note 8), containing a solution of 115 g. (0.50 mole) of dimethyl sebacate (Note 9) and 500 ml. of xylene (Note 5) is then inserted between the top of the condenser and the mercury valve. The air to the condenser is then turned on, and the electric mantle is turned off. The solvent is allowed to cool below its boiling point, and the stirrer is gradually brought to a stop. Throughout these operations the nitrogen flow is adjusted to keep air out of the system. Through a side neck is then added 50.6 g. (2.20 gram atoms) of crust-free sodium metal cut into lumps of convenient size. The side neck is closed, and the stirrer and the heater are turned on. The sodium is dispersed by stirring at about 6000–8000 r.p.m. for 10 minutes, and, with continued heating and stirring at a rate somewhat slower (to give suitable mixing), the dropwise addition of the ester solution is begun at such a rate as to be complete in about 24 hours (Notes 10 and 11).

Heating and stirring are continued for 1 hour after the addition is completed. The stirrer is then slowed, heating is stopped, the heater is removed, and the reaction flask is allowed to cool for about 15 minutes (Note 12). The reaction flask is then cooled in a water bath, and is finally thoroughly cooled in an ice bath. A solution of 140 ml. of glacial acetic acid in an equal volume of xylene is then added dropwise during about 30 minutes with continued cooling and stirring (Note 13). After addition of 450 ml. of water, stirring is stopped, the nitrogen is turned off, and the flask is disconnected from the apparatus. The two-phase mixture is filtered through a large Büchner funnel with suction to remove a small amount of gum, and the filtrate is then poured into a 3-l. separatory funnel. The aqueous phase is drawn off, extracted with 100 ml. of xylene, and is discarded. The xylene phases are washed in series with 100 ml. of water, and are combined and dried with 10 g. of anhydrous magnesium sulfate. The solution is filtered into a 3-l. round-bottomed flask, and the bulk of the xylene is distilled with the aid of an aspirator (Notes 14 and 15). The residue is transferred to a smaller flask and is distilled through a 2-ft. Vigreux column, the fraction boiling at 134–138°/14 mm. or 124–128°/9 mm. being collected as a yellowish liquid weighing 57–63 g. (67–74%). This material solidifies on standing and is sufficiently pure for most purposes (Notes 16 and 18). For further purification it may be crystallized from 150 ml. of pentane by cooling to −10° in an ice-salt bath for several hours. The mixture is filtered, and the crystals are washed with 50 ml. of pentane which has been cooled to −80°. The pure product thus obtained is a white granular crystalline solid, m.p. 38–39°, weighing 53–56 g. (63–66%) (Notes 17 and 18).

2. Notes

1. A flask having this shape gives the most efficient mixing.[2]

2. A one-fourth-horsepower motor is adequate. A suitable motor is manufactured by Bodine Electric Company, Chicago, Illinois.

3. The use of a water-cooled glass condenser is not recommended since it might accidentally be broken and thereby cause water to flow into the flask. A metal water-cooled condenser has also been used and is satisfactory.

4. Adapted from that described in *Org. Syntheses*, Coll. Vol. **2**, 129 (1943).

5. The xylene used was purified by heating under reflux with sodium overnight and then distilling, b.p. 137–142°.

6. Linde high-purity dry nitrogen was used without further treatment.

7. The fumes may be taken off by attaching an aspirator. This procedure assures removal of all moisture from the system.

8. The funnel is dried before use with a flame and is then closed with a drying tube and allowed to cool.

9. The ester used was Eastman Kodak Company technical grade shaken with sodium carbonate, dried and distilled. The ester boils at 158–160°/11 mm.

10. The reaction time can be lengthened considerably without effect. If, however, the time is shortened appreciably, the yield may be markedly lowered.

11. Initially the reaction may take on various colors, red, purple, etc., but after a short time a dull gray-brown color appears, which is gradually replaced by a yellow-brown or olive-drab color.

12. It is important that the reaction mixture be kept out of contact with the air until it has been acidified.

13. When sufficient acetic acid has been added, the dark color of the reaction mixture is replaced by a white color, and the mixture is often quite thick. More acetic acid is not harmful.

14. Nitrogen is led through the capillary during the distillations.

15. The xylene thus recovered is purified (Note 5) and is used in the next preparation.

16. This material slowly decomposes upon standing. It may be stored for at least several months with only slight decomposition if it is kept under nitrogen in the dark and at 0°. The compound appears to be stable when pure.

17. Homologs having a ring containing 10 to 18 carbons have been prepared in an analogous manner in yields from 46 to 85%.[6]

18. This preparation has also been carried out on a 1.0 mole scale by the checkers, using a 5-l. creased flask. Comparable yields are obtainable.

3. Methods of Preparation

Sebacoin has been prepared only by cyclization of methyl or ethyl sebacate with sodium metal.[3-8]

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[1] University of California, Los Angeles, California.

[2] Morton and Redman, *Ind. Eng. Chem.*, **40**, 1190 (1948).

[3] Hansley (to E. I. duPont de Nemours and Company), U. S. pat. 2,228,268 [*C. A.*, **35**, 2534 (1941)].

[4] Prelog, Frenkiel, Kobelt, and Barman, *Helv. Chim. Acta*, **30**, 1741 (1947).

[5] Stoll and Hulstkamp, *Helv. Chim. Acta*, **30**, 1815 (1947).

[6] Stoll and Rouvé, *Helv. Chim. Acta*, **30**, 1822 (1947).

[7] Blomquist, Burge, and Sucsy, *J. Am. Chem. Soc.*, **74**, 3636 (1952).

[8] Prelog, Schenker, and Günthard, *Helv. Chim. Acta*, **35**, 1598 (1952).

α-SULFOPALMITIC ACID

(Hexadecanoic acid, 2-sulfo-)

$$CH_3(CH_2)_{13}CH_2CO_2H + SO_3 \rightarrow CH_3(CH_2)_{13}CH(SO_3H)CO_2H$$

Submitted by J. K. Weil, R. G. Bistline, Jr., and A. J. Stirton.[1]
Checked by James Cason and Gerhard J. Fonken.

1. Procedure

Caution! Rubber gloves and a protective face shield should be worn while handling liquid sulfur trioxide, and the reaction should be carried out in a hood.

A 2-l. three-necked round-bottomed flask, with standard-taper ground-glass joints, is equipped for heating with an electric mantle or an oil bath, and fitted with a ball joint-sealed mechanical stirrer, a thermometer well, a graduated, pressure-equalizing dropping funnel, and a small vent. The dropping funnel, which should have a close-fitting stopcock well lubricated with heavy silicone grease, is placed so as to discharge sulfur trioxide well above the surface of the reaction mixture. Palmitic acid (200 g., 0.78 mole) (Note 1) and 600 ml. of carbon tetrachloride (Note 2) are added to the flask. Solution of the palmitic acid is endothermic and causes the temperature of the mixture to fall 5 to 10° below room temperature (Note 3). Stabilized liquid sulfur trioxide, 53 ml. (100 g., 1.25 moles) (Note 4), is added dropwise from the dropping funnel to the stirred mixture. Solution of palmitic acid becomes complete, the solution darkens, and the temperature rises to 45° as the sulfur trioxide is added over a 30-minute period. The reaction mixture is finally heated for 1 hour at 50–65° with continued stirring and is then chilled in an ice bath before the accessories are removed from the flask. The necks are closed with glass stoppers, and the reaction mixture is refrigerated at about −15° overnight (Note 5).

Crystallized solids are filtered by suction (Note 6), washed with cold carbon tetrachloride, and dried at room temperature in a vacuum desiccator to constant weight (1 to 2 days). The crude dark product weighs 197–223 g. (75–85%), and is usually satisfactory for the preparation of derivatives such as salts (Note 7) and esters.[2] One crystallization from acetone (7 ml./g.) at −20° yields a light gray solid, with neutralization equivalent within 1–2% of the theoretical value of 168, in a yield of 178–197 g. (68–75%). Two or three additional crystallizations (leaving a yield of only 25–30%) are required to give an almost colorless crystalline solid, m.p. 90–91° (Note 8). Once crystallized material is moderately stable to storage in a container protected from moisture, but slow darkening occurs, especially in presence of sunlight.

2. Notes

1. A purified fatty acid is recommended for the preparation of a pure α-sulfo acid. Purified palmitic acid (m.p. 60.8–61.4°, neutralization equivalent 256.2) is prepared by twice recrystallizing a good commercial grade of palmitic acid from acetone at 0°, using a solvent ratio of 10 ml. to 1 g. However, the reaction may be applied to commercial saturated higher fatty acids, if the iodine number is sufficiently low. The checkers obtained similar results with recrystallized Neo-Fat 1-56 (Armour and Company, Chicago, Ill.) or Eastman white label palmitic acid.

2. Other chlorinated solvents such as tetrachloroethylene or chloroform may be used in place of carbon tetrachloride. *Caution!* The reaction of sulfur trioxide with chlorinated solvents has been reported[3] to give phosgene and other toxic products. Adequate venting of all by-product gases is essential.

3. The mixture which is a slurry at 15° may be used or it may be warmed to about 30° to give a clear solution. If the slurry is warmed before sulfur trioxide addition, it is usually not necessary to heat after all of the sulfur trioxide has been added.

4. Liquid sulfur trioxide may be purchased in stabilized form as Sulfan B,[4] m.p. 17°, b.p. about 45°. Caution must be exercised in handling sulfur trioxide. The liquid is highly corrosive to the skin and the vapor may cause injury if inhaled. The powerful oxidizing and dehydrating effects of sulfur trioxide should not be underestimated. The liquid may be stored in a glass-stoppered bottle if the stopper is lubricated with a heavy silicone grease. Because the liquid reacts violently with water the bottle lip should be wiped free of any moisture to avoid spattering when the liquid is poured. If solidification of sulfur trioxide should occur as the result of hydration, the vented (Hood!) solid may be liquefied by gentle application of heat from an infrared lamp.

5. Shorter refrigerating periods at temperatures up to +5° give slightly lower yields.

6. Since the mixture filters rather slowly, even after storage overnight, a Büchner funnel of at least 20 cm. diameter should be used, and a hard grade of filter paper (such as Whatman no. 50) is recommended. Use of a rubber dam helps to express solvent and exclude moisture from the hygroscopic product.

7. The monosodium salt $CH_3(CH_2)_{13}CH(SO_3Na)CO_2H$ may be prepared by neutralizing only the sulfonic acid group or by adding aqueous sodium sulfate to a hot aqueous solution of the crude α-sulfo acid and cooling to room temperature. The monosodium salt crystallizes in white plates, leaving most of the color in the filtrate. The disodium salt is formed by further neutralization with sodium hydroxide.

8. α-Sulfolauric, α-sulfomyristic, α-sulfostearic, and α-sulfobehenic acids have been prepared by this procedure. The table shows the melting point and neutralization equivalent after at least four recrystallizations and a 12-hour drying period at 76° under 1 mm. pressure. There is some uncertainty in the melting points because of the hygroscopic character of the α-sulfo acids.

	Neutralization Equivalent		
	Found	Theoretical	M.P.
α-Sulfolauric acid	142	140.4	86.5–88°
α-Sulfomyristic acid	154	154.2	85–86.5°
α-Sulfopalmitic acid	171	168.2	90–91°
α-Sulfostearic acid	182	182.2	96–97°
α-Sulfobehenic acid	212	210.3	95–97°

3. Methods of Preparation

Other direct methods for the sulfonation of the higher fatty acids are by the use of sulfur trioxide vapor [5] or by the use of chlorosulfonic acid.[6] Indirect methods are also available for the preparation of α-sulfo fatty acids and their salts from an α-bromo fatty acid made by the Hell-Volhard-Zelinsky reaction. The bromo compound may be converted directly to the sodium salt of a sulfonic acid through the Strecker reaction [7] or may be converted to the mercaptan and oxidized to the sulfonate.[8] Sulfonation of the lower fatty acids has been studied by Backer and co-workers.[9]

α-Sulfonation with sulfur trioxide appears to be generally applicable to carboxylic acids having an α-methylene group.

[1] Eastern Regional Research Laboratory, Philadelphia 18, Pennsylvania, a laboratory of the Eastern Utilization Research Branch, Agricultural Research Service, U. S. Department of Agriculture, Philadelphia 18, Pennsylvania.

[2] Weil, Bistline, and Stirton, *J. Am. Chem. Soc.*, **75**, 4859 (1953).

[3] "Reactions of SO_3," Tech. Service Bull. SF-2, General Chemical Division, Allied Chemical and Dye Corporation, 40 Rector Street, New York 6, N. Y.

[4] "Storage, Handling and Use of Sulfan," Tech. Service Bull. SF-3, General Chemical Division, Allied Chemical and Dye Corporation.

[5] Günther (1932), PB30081, Office of Tech. Services, U. S. Department of Commerce; *Bibliography of Scientific and Industrial Reports*, **4**, 662 (1947).

[6] Günther and Hetzer (to I. G. Farbenindustrie A.-G.), U. S. pat. 1,926,442 [*C. A.*, **27**, 6001 (1933)].

[7] Mehta and Trivedi, *Melliand Textilber.*, **21**, 117, 288 (1940) [*C. A.*, **34**, 6087 (1940)].

[8] Weil, Witnauer, and Stirton, *J. Am. Chem. Soc.*, **75**, 2526 (1953).

[9] *E.g.*, de Boer, *Rec. trav. chim.*, **71**, 814 (1952).

TETRAETHYLTIN

(Tin, tetraethyl-)

$$4C_2H_5Br + 4Mg \rightarrow 4C_2H_5MgBr$$

$$SnCl_4 + 4C_2H_5MgBr \rightarrow (C_2H_5)_4Sn + 2MgCl_2 + 2MgBr_2$$

Submitted by G. J. M. Van Der Kerk and J. G. A. Luijten.[1]
Checked by M. S. Newman and L. L. Wood.

1. Procedure

A 2-l. three-necked flask is fitted with a reflux condenser (Note 1), a stirrer (Note 2), and a dropping funnel. The flask is suspended in a steam cone, which can also be used as a cooling bath. In the flask is placed 50 g. (2.05 gram atoms) of fine magnesium turnings (Note 3). In the dropping funnel is first introduced 5 ml. of a solution of 250 g. (175 ml., 2.3 moles) of ethyl bromide in 500 ml. of absolute ether. Three drops of bromine is mixed with the 5 ml., and the mixture is added to the magnesium. The Grignard reaction which starts at once (Note 4) is maintained by gradually adding the remainder of the ethyl bromide-ether solution. When the spontaneous reaction subsides, the mixture is heated gently under reflux with stirring for 30 minutes.

The flask is then cooled in ice, and in the course of about 20 minutes 83 g. of tin tetrachloride (37 ml., 0.32 mole) is added with vigorous stirring (Note 5). The mixture is heated at the reflux temperature for 1 hour, after which the condenser is set for distillation. During 1.5 hours the ether is removed by distillation while the flask is heated by an ample supply of steam (Notes 6 and 7).

The flask is again cooled in ice, the collected ether is returned to the reaction mixture, and the latter is decomposed by slowly adding first 85 ml. of ice water, then 400 ml. of ice-cold 10% hydrochloric acid. After stirring for some minutes, the contents of the flask are transferred to a separatory funnel. The layers are separated, and the ether layer is filtered through a folded filter and dried with calcium chloride (Note 8).

The ether is removed by distillation, and the crude tetraethyltin is distilled under water-pump vacuum, using a water bath for heating. The yield of tetraethyltin boiling at 63–65°/12 mm. is 67–72 g. (89–96%), n_D^{25} 1.4693–1.4699, d_4^{25} 1.1916 [7] (Note 9).

2. Notes

1. A wide condenser must be employed to permit an ample reflux of ether.
2. A seal is recommended as described in *Org. Syntheses*, Coll. Vol. **3**, 368 (1955), Note 1.
3. The submitters have carried out this preparation on a three-fold scale with comparable yields.
4. In general bromine starts Grignard reactions more quickly than the usually employed iodine.
5. For adding the tin tetrachloride it is advisable to use a dropping funnel which contains no ether vapor, since the latter gives troublesome formation of solid etherate.
6. The stirrer must be stopped at the beginning of the distillation or it will break, for the contents of the flask turn into a solid mass.
7. Removal of the ether is necessary to permit raising the reaction temperature. The temperature at the center of the mass reaches 60–65°. During the 1.5 hours of distillation, about 200 ml. of ether is collected, the remainder being firmly bound as etherates.
8. To obtain a product free from traces of triethyltin halide the dried ethereal solution is treated with dry ammonia, and the precipitate formed is removed by filtration.
9. The submitters report that the same yields in terms of percentages are obtained if the procedure is applied to the preparation of tetra-*n*-propyltin and tetra-*n*-butyltin.

3. Methods of Preparation

Tetraethyltin has been prepared from tin-sodium alloy and ethyl iodide,[2] from tin-sodium-zinc alloy and ethyl bromide,[3,4] and from tin tetrachloride and ethylmagnesium bromide.[5,6,7] The method described is essentially that of Pfeiffer and Schnurmann.[5]

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[1] Organisch Chemisch Instituut T.N.O., Utrecht, The Netherlands.

[2] Löwig, *Ann.*, **84**, 317 (1852).

[3] Harada, *Sci. Papers Inst. Phys. Chem. Research Tokyo*, **35**, 290 (1939) [*Chem. Zentr.*, **1939**, II, 2912].

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[5] Pfeiffer and Schnurmann, *Ber.*, **37**, 319 (1904).

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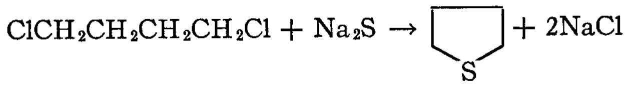
TETRAHYDROTHIOPHENE

(Thiophene, tetrahydro-)



Submitted by J. Keith Lawson, William K. Easley, and William S. Wagner.[1]
Checked by William S. Johnson and W. David Wood.

1. Procedure

A 5-l. round-bottomed three-necked flask equipped with a mechanical stirrer, a reflux condenser (Note 1), and two 250-ml. dropping funnels (mounted with the aid of a Y-tube) is charged with 1.7 l. of dimethylformamide (Note 2). The flask is heated until the dimethylformamide is almost refluxing. Then, with stirring, 280 ml. (318 g., 2.5 moles) of 1,4-dichlorobutane and a solution of 359 g. (2.75 moles) of 60% sodium sulfide (Note 2) in 1 l. of hot water are added simultaneously from the dropping funnels at such a rate that the mixture refluxes without application of heat (Note 3). After the addition is complete (about 1.5 hours), the mixture is heated at reflux with stirring for an additional 2 hours. The condenser is arranged for distillation, and 600 ml. of distillate is collected (Note 4). The distillate is made alkaline by adding 20 g. of sodium hydroxide, and sodium chloride is added to the saturation point. The aqueous layer is separated and discarded, and the crude tetrahydrothiophene layer is dried over solid potassium hydroxide. Distillation through a 30-cm. Vigreux column gives, after a small fore-run

(Note 5), 160–172 g. (73–78%) of colorless tetrahydrothiophene, b.p. 119–121°, n_D^{25} 1.5000–1.5014 (Notes 6 and 7).

2. Notes

1. The reaction should be carried out in a hood, or the outlet of the condenser should be connected to a fume trap.

2. Technical grade DMF is available from the Grasselli Chemicals Department of E. I. duPont de Nemours and Company. The 1,4-dichlorobutane was obtained from the Electrochemicals Department, E. I. duPont de Nemours and Company. Technical Baker and Adamson fused chip sodium sulfide assaying 60% sodium sulfide was used. The checkers obtained somewhat lower yields when the appropriate amount of reagent grade $Na_2S \cdot 9H_2O$ was employed instead of the technical material.

3. The addition of the reactants takes approximately 1.3 hours and should be carried out so that the addition of both reactants is completed at approximately the same time.

4. The dimethylformamide solution may be used repeatedly if each time the volume is reduced by the distillation of the remaining water. After two runs the accumulated sodium chloride should be removed by filtration.

5. A small amount of dimethylamine is always present in the crude product. This is removed before collection of the product by operating the column under total reflux for 1–2 hours. The vent of the still head should be connected to a hood during this operation. If foaming does not subside after this treatment the use of a 1-l. still pot is indicated.

6. When several runs are made, an additional amount of the product can be obtained by redrying and redistilling the foreruns. The submitters have obtained yields as high as 90% on a larger-scale operation.

7. The reaction may also be carried out in aqueous medium with an increase in the time of reaction to 4 hours. By this method the submitters obtained a 78% yield on a large-scale run. When only a single run is to be made, this procedure may be preferred as a matter of economy.

3. Methods of Preparation

Tetrahydrothiophene has been prepared by the reaction of 1,4-diiodobutane and potassium sulfide,[2] by the reaction of 1,4-dibromobutane and sodium sulfide,[3,4] by the reaction of tetramethylene glycol and hydrogen sulfide in the presence of alumina at high temperature,[5] by the reaction of tetrahydrofuran and hydrogen sulfide in the presence of alumina at high temperature,[6] and by the hydrogenation of thiophene with molybdenum disulfide [7] or palladium on charcoal [8] as catalysts.

---

[1] The Chemstrand Corporation, Decatur, Alabama.

[2] von Braun and Trümpler, *Ber.*, **43**, 545 (1910).

[3] Grishkevich-Trokhimovskii, *Zhur. Russ. Fiz. Khim. Obshchestva*, **48**, 901 (1916) [*C. A.*, **11**, 785 (1917)].

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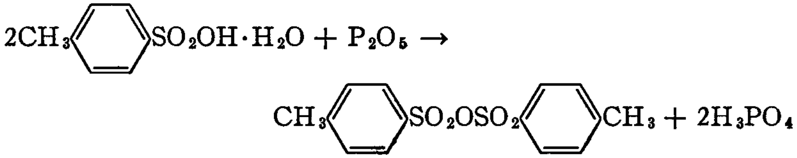
[5] Yur'ev and Medovshchikov, *Zhur. Obshcheĭ Khim.*, **9**, 628 (1939) [*C. A.*, **33**, 7779 (1939)].

[6] Yur'ev and Prokina, *Zhur. Obshcheĭ Khim.*, **7**, 1868 (1937) [*C. A.*, **32**, 548 (1938)].

[7] Cawley and Hall, *J. Soc. Chem. Ind. London*, **62**, 116 (1943).

[8] Mozingo, Harris, Wolf, Hoffhine, Easton, and Folkers, *J. Am. Chem. Soc.*, **67**, 2092 (1945).

p-TOLUENESULFONIC ANHYDRIDE



Submitted by L. Field and J. W. McFarland.[1]
Checked by William S. Johnson, Raymond R. Hindersinn, and A. G. Fisher.

1. Procedure

A mixture of 213 g. (1.5 moles) of phosphorus pentoxide and 14 g. of kieselguhr (Note 1) is prepared by shaking in a dry, stoppered 1-l. Erlenmeyer flask. About one-half of the mixture is then added to a mixture of 7 g. of asbestos (Note 1) and 190 g.

(1.0 mole) of *p*-toluenesulfonic acid monohydrate (Note 2) in a 1-l. round-bottomed flask with one standard-taper neck protected from atmospheric moisture with a drying tube containing calcium chloride. The mixture, which soon becomes quite hot, is allowed to stand for 1 hour with occasional swirling. It is then heated in an oil bath held at about 125° for 9 hours, the remainder of the phosphorus pentoxide mixture being added in four portions during the first 3 hours. During this total 9-hour period the mass is mixed as well as possible with a metal spatula from time to time.

The drying tube is replaced by a condenser, and 400 ml. of ethylene chloride (Note 3) is added. The mixture is heated under reflux for several minutes. The flask is closed with a glass stopper and shaken well (Note 4). A thin pad of glass wool is then inserted into the lower part of the flask neck, and the extract is decanted. This extraction and decantation process is repeated with three 100-ml. portions of ethylene chloride. The extracts are combined in a 1-l. round-bottomed flask, the solvent is removed by distillation under reduced pressure, and the molten solid is swirled briefly at 3 mm. pressure until cessation of bubbling indicates complete removal of solvent. The dark oily solid, which is formed on cooling, amounts to 138–143 g. and melts in the range 80–124° (sealed tube) (Note 5). This material is purified by dissolving it in the minimum amount (about 200 ml.) of boiling anhydrous benzene (Notes 6 and 7) and, after cooling to about 50°, adding 300 ml. of anhydrous ether (Note 7). After crystallization is well advanced, the mixture is stored at −5° overnight. The solvent is removed by forcing it under nitrogen pressure either through a 6-mm. glass tube packed with glass wool up to a constriction about 1 in. from the bottom or through a sintered-glass filter stick. Residual solvent is removed at 3-mm. pressure through a stopcock which is then closed to permit storage of the anhydride at low pressure (Note 8). The yield is 77–114 g. (47–70%) of light brown or gray prisms. The product, which softens at about 90° and melts at 110–127° (sealed tube) (Note 5), is sufficiently pure for most purposes (Note 9).

2. Notes

1. It is satisfactory to use the "Super-Cel" brand of kieselguhr supplied by Johns-Manville Company and asbestos of the type used in Gooch crucibles. Inclusion of these inert materials facilitates mixing and extraction of the product.

2. A good commercial grade of *p*-toluenesulfonic acid monohydrate, m.p. 104–106°, was used.

3. A good commercial grade of ethylene chloride, b.p. 83–84°, was used. It is dried by distilling a portion.

4. If shaking is too violent, the gummy residue that clings to the flask may be dislodged, and the flask may break. After extraction is complete, the phosphorus pentoxide residue can be removed from the flask by adding water and replacing this by fresh water as the mixture becomes hot.

5. Even brief exposure to moist air causes a lowering of the melting point. The melting-point tube is therefore best filled by inserting it into material ground against the flask bottom or by using a dry box; the tube is then quickly sealed. The melting point of pure *p*-toluenesulfonic anhydride is 129.5–131.5°, with softening about 120° (sealed tube).[2]

6. Commercial grades of anhydrous ether and benzene which have been allowed to stand over sodium are satisfactory. Dry glassware should be used for transferring the solvents.

7. Usually a small amount of material remains undissolved. This material does not affect the melting point significantly but can be removed if desired by forcing the solution, kept hot by an electric heating mantle, through the filter arrangement described above into a dry flask protected from moisture by a calcium chloride tube.

8. In order to open the flask, air is admitted slowly through a calcium chloride tube. The melting point of the anhydride drops somewhat during prolonged storage with occasional opening, but the purity does not seem to be affected appreciably.[2]

9. The broad melting range apparently results from an unusual sensitivity of this property to small amounts of impurities.[2] The melting point can be raised by further recrystallizations.

3. Methods of Preparation

p-Toluenesulfonic anhydride has been prepared from the acid by the use of thionyl chloride [3] and phosphorus pentoxide.[2] It has also been obtained by heating oxime *p*-toluenesulfonates,[4] by reaction of *p*-toluenesulfonic acid with di-*p*-tolylcarbodiimide,[5] and by the interaction of methoxyacetylene and *p*-toluenesulfonic acid.[6]

---

[1] Department of Chemistry, Vanderbilt University, Nashville 4, Tennessee.

[2] Field, *J. Am. Chem. Soc.*, **74**, 394 (1952).

[3] Meyer and Schlegl, *Monatsh. Chem.*, **34**, 573 (1913); Meyer, *Ann.*, **433**, 335 (1923).

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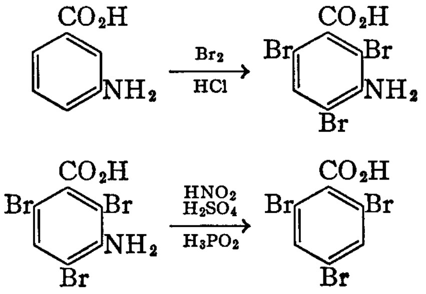
[6] Eglinton, Jones, Shaw, and Whiting, *J. Chem. Soc.*, **1954**, 1864.

2,4,6-TRIBROMOBENZOIC ACID

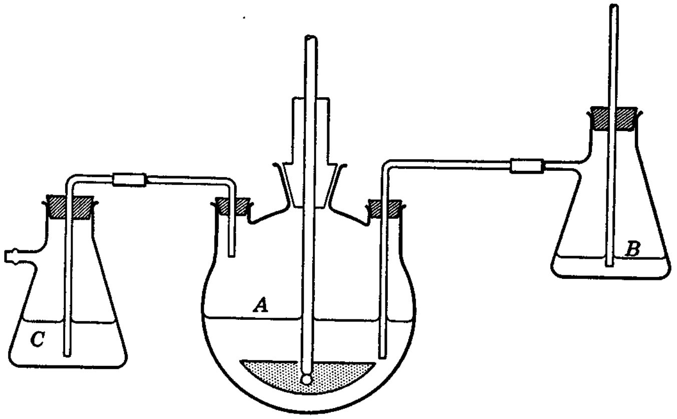
(Benzoic acid, 2,4,6-tribromo-)



Submitted by Michael M. Robison and Bonnie L. Robison.[1]
Checked by N. J. Leonard and Kenneth Conrow.

1. Procedure

A. *3-Amino-2,4,6-tribromobenzoic acid.* The bromination apparatus consists of a 2-l. three-necked standard-taper flask *A*, equipped with a "Trubore" stirrer and attached by rubber stoppers and glass tubing to two filter flasks, *B* and *C*, as shown



in the diagram. The 250-ml. flask *C*, which serves as a bubbler and trap, is half-filled with water, and its side-arm is connected to a water pump. The reaction flask *A* is charged with 27.4 g. (0.2 mole) of *m*-aminobenzoic acid (Note 1), 165 ml. of concentrated hydrochloric acid, and 780 ml. of water, after which it is surrounded by an ice bath, and the stirrer is started. One hundred-forty grams (45 ml., 0.88 mole) of bromine is placed in the vaporization flask *B*, which is then surrounded by a water bath heated to 40–50°. Bromine vapor is drawn through the reaction mixture at a moderate rate by applying suction at the water pump. Stirring and cooling of the mixture are continued throughout the reaction period, during which time the product precipitates (Note 2). The bromination requires about 3 hours and is complete when the slurry assumes a distinct yellow color.[2]

The cream-colored solid is separated at once by filtration and washed thoroughly with water to remove excess bromine water and acids. It is used in the next step without drying. The melting range of the crude product is usually 170–172°.

B. *2,4,6-Tribromobenzoic acid.* A 5-l. three-necked flask, equipped with a mechanical stirrer and thermometer and surrounded by an ice-salt bath, is charged with a precooled mixture of 1.02 l. of concentrated sulfuric acid and 500 ml. of water. Cooling during the reaction period is assisted by the ice-salt bath, but is effected chiefly by periodic additions of large amounts of crushed Dry Ice directly to the reaction mixture. The temperature of the stirred mixture is lowered to −5° to −10°, and 37 g. (0.54 mole) of sodium nitrite is added in small portions over a period of about 15 minutes. Cold 50% hypophosphorous acid (193 ml., 1.86 moles) (Note 3) is then added over a period of 10–15 minutes, the temperature still being maintained below −5°. A solution of the bromination product in 1.85 l. of glacial acetic acid is then added to the stirred diazotizing solution from a dropping funnel. During the 1–1.25 hours required to complete this addition the temperature is held between −10° and −15° (Note 4). Stirring of the slurry is continued for approximately 2 hours longer, and during this period the temperature is allowed to rise gradually to +5°. The loosely stoppered flask is kept in a refrigerator for 36 hours (Note 5), during which time nitrogen and some oxides of nitrogen are evolved (Caution!). Most of the acetic acid is then removed by volatilization in a current of steam, 3 liters of distillate being collected. During the steam distillation the product starts to precipitate from the clear solution, and nitrogen dioxide and some hydrogen sulfide are given off. The residual liquid is cooled, and the product is collected on a sintered-glass funnel and washed with water. It is next suspended in 800 ml. of water, and approximately 9 g. of anhydrous sodium carbonate is added with shaking to bring it into solution. The yellow liquid is filtered to remove small quantities of insoluble impurities, and the acid is reprecipitated by acidification to *p*H 1–2 with 5% hydrochloric acid, while swirling vigorously. The cream-colored precipitate is separated by filtration, washed with water, and dried. The yield of 2,4,6-tribromobenzoic acid, sufficiently pure for preparative purposes, is 50–57.5 g. (70–80%), m.p. 192.5–194.5° (Note 6).

2. Notes

1. Matheson Company *m*-aminobenzoic acid was used without further purification.
2. Efficient stirring and cooling are necessary at this stage to obtain a final product that is not colored.

3. Baker "purified" hypophosphorous acid was used.
4. Near the end of the addition of the acetic acid solution it is usually desirable to raise the stirrer temporarily to break up the lumps which form at the surface of the solution.
5. The temperature of the refrigerator was approximately 6°.
6. The product may be recrystallized from 1:2 acetic acid-water (about 8 ml./g.), but this process effects little improvement in melting point or color, even when activated carbon is used.

3. Methods of Preparation

2,4,6-Tribromobenzoic acid has been prepared by the deamination of 2,4,6-tribromo-3-aminobenzoic acid (reagents not specified),[3] by hydrolysis of 2,4,6-tribromobenzonitrile,[4-7] and by oxidation of the tribromotoluene,[8,9] the benzyl chloride,[10] the aldehyde,[11] and the glyoxylic acid.[12] The present method is a modification of that of Bunnett, Robison, and Pennington.[13]

[1] Chemistry Department, Amherst College, Amherst, Massachusetts.

[2] This is the method of Coleman and Talbot, *Org. Syntheses*, Coll. Vol. **2**, 592 (1943), for 2,4,6-tribromoaniline.

[3] Hübner, *Ber.*, **10**, 1708 (1877).

[4] Sudborough, *Ber.*, **27**, 512 (1894).

[5] Wegscheider, *Monatsh. Chem.*, **18**, 218 (1897).

[6] Sudborough, Jackson, and Lloyd, *J. Chem. Soc.*, **71**, 230 (1897).

[7] Montagne, *Rec. trav. chim.*, **27**, 351 (1908).

[8] Asinger, *J. prakt. Chem.*, **142**, 291 (1935).

[9] Cohen and Dutt, *J. Chem. Soc.*, **105**, 516 (1914).

[10] Henraut, *Bull. soc. chim. Belg.*, **33**, 132 (1924).

[11] Blanksma, *Chem. Weekblad*, **9**, 865 (1912) [*Chem. Zentr.*, **1912**, II, 1965].

[12] Fuchs, *Monatsh. Chem.*, **36**, 137 (1915).

[13] Bunnett, Robison, and Pennington, *J. Am. Chem. Soc.*, **72**, 2378 (1950).

SUBJECT INDEX

(This cumulative index comprises material from Volumes 30, 31, 32, 33, 34, 35, and 36; 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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