3-ACETYLOXINDOLE

(Oxindole, 3-acetyl-)

$$2K + 2NH_3 \rightarrow 2KNH_2 + H_2$$
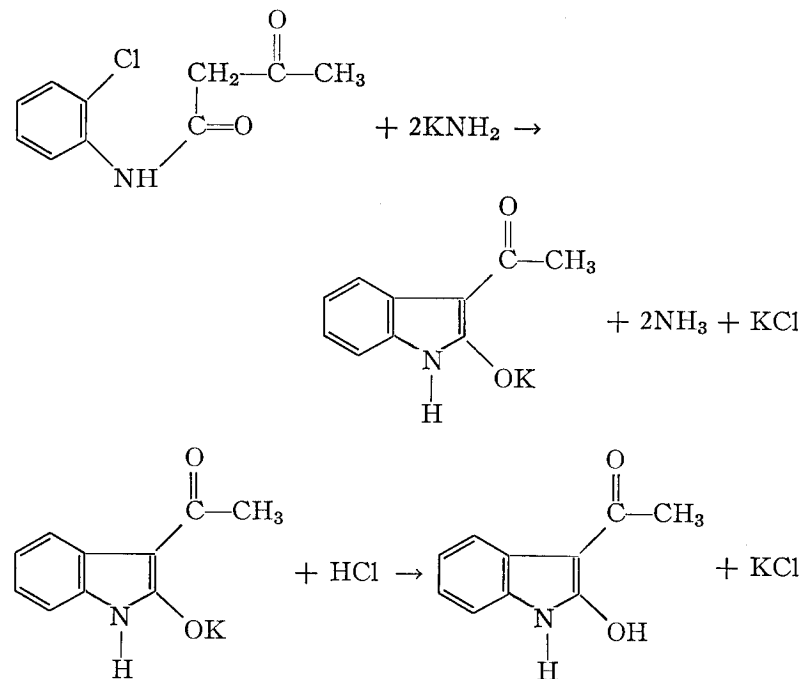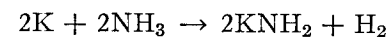
Submitted by J. F. BUNNETT, B. F. HRUTFIORD and S. M. WILLIAMSON.[1]
Checked by B. C. McKUSICK and D. C. BLOMSTROM.

1. Procedure

An apparatus resembling that pictured by Schlatter[2] is assembled in a good hood. Two 5-l. three-necked flasks are mounted side by side about 10 cm. apart and about 10 cm. above the bench top or stand base. These are referred to as the "left" and "right" flasks. Each flask is provided with a dry ice condenser in the outermost neck, and each condenser is protected from the

air by a soda-lime drying tube. Each flask is provided through the center neck with a motor-driven stirrer. The left stirrer should have a large sweep blade, and the right stirrer should have a small propeller-type blade. The bearing on each stirrer should be capable of holding a small positive pressure (the submitters used ball-joint bearings). The innermost neck of each flask is fitted with a two-holed rubber stopper. One hole in each stopper is for nitrogen supply; a short piece of glass tubing is inserted through each stopper, and these pieces of glass tubing are connected by rubber tubes to a glass "Y" tube which in turn is connected by rubber tubing to a tank of dry nitrogen. The rubber tubes between the "Y" tube and the flasks are provided with pinch clamps so that the flow of nitrogen can be directed into either flask or into both at once. The other hole in each stopper is for transfer of liquid ammonia from the right flask to the left. A glass tube reaching to the very bottom of the right flask is inserted through the right stopper. A glass tube is inserted through the left stopper so that it projects only a few centimeters into the left flask. These glass tubes are bent so that they point toward each other, and they are connected by a piece of rubber tubing provided with a pinch clamp.

With nitrogen flowing and all pinch clamps open, the apparatus is flamed to drive away traces of moisture. The condensers are then provided with dry ice covered by isopropyl alcohol, and the lower part of the right flask is embedded in crushed dry ice. Liquid ammonia (4 l.) is introduced into the right flask through the nitrogen inlet from which the rubber tubing is temporarily disconnected, and 105.8 g. (0.5 mole) of o-acetoacetochloroanilide (Note 1) is placed in the left flask. In order to destroy any water in the ammonia, the right stirrer is started and small pieces of potassium metal are dropped into the ammonia, by briefly lifting the right two-holed stopper, until the blue color persists for 3 minutes. The nitrogen connection to the left flask is clamped shut and, by partially blocking the escape of nitrogen from the right drying tube, about 1 l. of ammonia is forced into the left flask. The connection between the two flasks is now clamped shut. Brief operation of the left stirrer facilitates solution of the o-acetoacetochloroanilide in the ammonia.

Potassium metal (78 g.; 2 moles) is cut into chunks just small enough to pass through the neck of the right flask; these are stored in a beaker under xylene until needed. About 5 g. of potassium is introduced into the right flask by briefly lifting the two-holed stopper. The right stirrer is started and the potassium is allowed to dissolve. To the resulting deep blue solution is added 0.1 g. of finely crushed ferric nitrate hydrate, a catalyst for the reaction of potassium with ammonia. The solution should begin to boil with evolution of hydrogen. (*Caution: No flames or sparks should be nearby.*) The rest of the potassium is added at such a rate as to maintain active gas evolution (Note 2). Stirring is continued in the right flask until all the potassium is consumed, i.e., until the blue color disappears. The right flask now contains a solution of potassium amide in liquid ammonia; 30–60 minutes is required for its preparation.

The tube between the two flasks is opened by releasing the pinch clamp, and the left stirrer is started. With nitrogen flow to the left flask still blocked, the potassium amide solution is caused to flow into the left flask by partially blocking the right nitrogen exit. The solution in the left flask slowly assumes a chartreuse color. As soon as the right flask is as nearly empty as the apparatus will permit, nitrogen flow is opened to the left flask and closed to the right flask and the connection between the two flasks is clamped shut. The right flask is then disconnected and immediately cleaned by rinsing it carefully with ethyl or isopropyl alcohol to destroy potassium amide and then washing it with water. (*Caution: Potassium amide is inflammable and will ignite on contact with moisture.*)

The solution in the left flask is stirred for 30 minutes after all the potassium amide has been added. The nitrogen inlet is briefly removed and 120 g. (1.5 moles) of ammonium nitrate is added; this discharges the chartreuse color. (*Caution: Vigorous foaming occurs.*) Ethyl ether (500 ml.) is added and the dry ice condenser is replaced by a standard water-cooled condenser. The ammonia is evaporated by allowing the stirred reaction mixture to warm to room temperature; this takes several hours and it is convenient to have it occur overnight.

Water (1.5 l.) is added and the mixture is transferred to a

separatory funnel. The lower aqueous layer, which contains the potassium salt of 3-acetyloxindole, is separated and is then extracted with ethyl ether three times to remove a purple impurity. The aqueous layer is then made acidic to litmus by addition of hydrochloric acid; this causes precipitation of crude, tan-colored 3-acetyloxindole. The mixture is chilled, and the product is collected by suction filtration and washed well on the filter with water. The yield of crude 3-acetyloxindole, m.p. 204–206°, is 65–68 g. (74–78%). It may be purified by recrystallizing it from 1.7 l. of chloroform in the presence of 2 g. of decolorizing carbon. A heated filter funnel must be used in separating the carbon because the product starts to crystallize only slightly below the boiling point of chloroform. The recrystallized 3-acetyloxindole weighs 53–59 g. (61–67%) and is in the form of white needles, m.p. 204–205.5°.

2. Notes

1. The *o*-acetoacetochloroanilide used was the technical product of Union Carbide Chemicals Co.; m.p. 107–109°.

2. If the reaction of potassium with liquid ammonia slows down before all the potassium is consumed, an additional pinch of ferric nitrate hydrate is added.

3. Methods of Preparation

3-Acetyloxindole has been made by condensing ethyl acetate with oxindole in the presence of sodium ethoxide [3] and by heating N-acetyloxindole with sodium amide in xylene.[4] The present method was developed by Hrutfiord and Bunnett.[5] It illustrates a general principle for the synthesis of heterocyclic and homocyclic compounds. This principle involves the creation of an intermediate species that is of the benzyne type and has a nucleophilic center located so that it can add, intramolecularly, to the "triple bond" of the benzyne structure. Other applications of the principle using essentially the present procedure are the conversion of thiobenz-*o*-bromoanilide or thiobenz-*m*-bromoanilide to 2-phenylbenzothiazole (90% and 68% respectively);

of benz-*o*-chloroanilide to 2-phenylbenzoxazole (69%); and of 2-amino-2'-bromodiphenyl sulfide to phenothiazine (35%).[5]

[1] University of North Carolina, Chapel Hill, North Carolina.
[2] M. Schlatter, *Org. Syntheses*, Coll. Vol. **3**, 223 (1955).
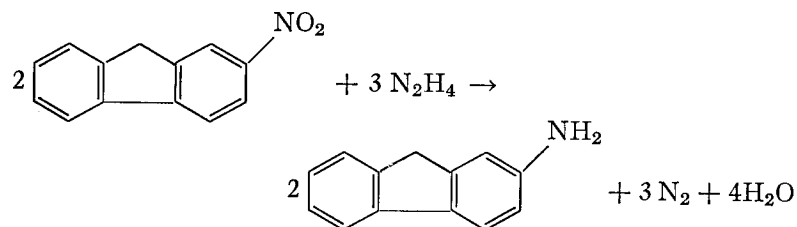[3] L. Horner, *Ann.*, **548**, 131 (1941).
[4] H. Behringer and H. Weissauer, *Ber.*, **85**, 774 (1952).
[5] B. F. Hrutfiord and J. F. Bunnett, *J. Am. Chem. Soc.*, **80**, 2021 (1958).

2-AMINOFLUORENE

(2-Fluorenylamine)

$$\text{2 (fluorene-NO}_2\text{)} + 3 N_2H_4 \rightarrow \text{2 (fluorene-NH}_2\text{)} + 3 N_2 + 4 H_2O$$

Submitted by P. M. G. Bavin.[1]
Checked by John C. Sheehan and Roger E. Chandler.

1. Procedure

In a 2-l. three-necked round-bottomed flask, equipped with a mechanical stirrer (Note 1), reflux condenser, and dropping funnel, are placed 30 g. of pure 2-nitrofluorene, m.p. 157° [*Org. Syntheses*, Coll. Vol. **2**, 447 (1943)], and 250 ml. of 95% ethanol. After warming to 50° on a steam bath, 0.1 g. of palladized charcoal catalyst (previously moistened with alcohol) is added (Note 2) and the stirrer is started. About 15 ml. of hydrazine hydrate is added from the dropping funnel during 30 minutes (Note 3). At this point an additional 0.1 g. of catalyst (previously moistened with alcohol) is added and the mixture is heated until the alcohol refluxes gently. After 1 hour the nitrofluorene has dissolved completely and the supernatant liquor is almost colorless.

The catalyst is removed by filtration with gentle suction through a thin layer of Celite (Note 4). The flask is rinsed with

30 ml. of hot alcohol which is then used to wash the catalyst and Celite. The combined filtrates are concentrated under reduced pressure to about 50 ml. (Note 5) and then heated to boiling at atmospheric pressure. When 250 ml. of hot water is added slowly, 2-aminofluorene is precipitated as a colorless, crystalline powder. After cooling in an ice bath, the 2-aminofluorene is collected, washed with water, and dried in the dark in a vacuum desiccator. The product melts at 127.8–128.8° (Note 6) and amounts to 24–25 g. (93–96%).

2. Notes

1. If the stirring is omitted, the nitrofluorene takes longer to dissolve.

2. A suitable catalyst is 10% palladium-on-charcoal, such as is supplied by Baker and Company, Inc., 113 Astor Street, Newark 5, New Jersey.

3. The reaction is exothermic, and too rapid addition of the hydrazine may cause the mixture to foam out of the condenser.

4. *Caution! The catalyst is often pyrophoric and should be kept moistened with alcohol.* Celite is a diatomaceous earth filter aid.

5. A rotary evaporator is very convenient for the concentration since some of the amine invariably crystallizes toward the end.

6. The melting point is that reported in *Organic Syntheses*, Coll. Vol. **2**, 448 (1943), for a recrystallized sample.

3. Methods of Preparation

The preparation of 2-aminofluorene reported previously in *Organic Syntheses* [Coll. Vol. **2**, 448 (1943)] was based on the method of Diels.[2]

The procedure given is based on the method first developed by Pietra[3] and applied by Dewar and Mole[4] to polycyclic compounds. It gives excellent yields of toluidines, aminobiphenyls, phenylenediamines, aminophenols, *p*-aminobenzoic acid, and similar compounds,[3,5] but it is not suitable for the reduction of some chloronitrobenzenes.[5] When applied to azobenzene and azoxybenzene it gives hydrazobenzene in 80–90% yield.[5]

Raney nickel may be used instead of palladized charcoal as the catalyst.[6]

[1] National Research Council of Canada Post-doctorate Fellow, 1954–56, at the University of Ottawa, Ottawa, Ontario. Present address: Smith, Kline and French Ltd., Welwyn Garden City, Herts, England.

[2] O. Diels, *Ber.*, **34**, 1758 (1901).

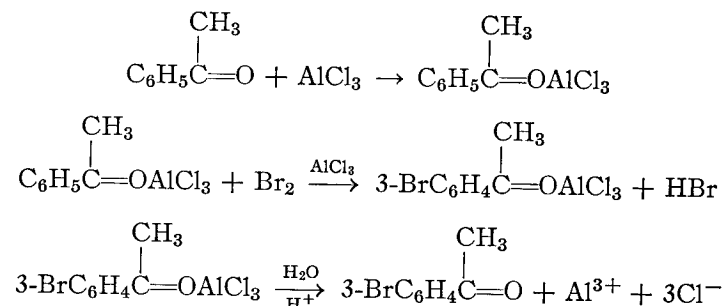[3] S. Pietra, *Ann. chim.* (Rome), **45**, 850 (1955).

[4] M. J. S. Dewar and T. Mole, *J. Chem. Soc.*, **1956**, 2556.

[5] P. M. G. Bavin, *Can. J. Chem.*, **36**, 238 (1958).

[6] D. Balcom and A. Furst, *J. Am. Chem. Soc.*, **75**, 4334 (1953).

3-BROMOACETOPHENONE

(Acetophenone, 3-bromo-)

$$C_6H_5\overset{\underset{|}{CH_3}}{C}{=}O + AlCl_3 \rightarrow C_6H_5\overset{\underset{|}{CH_3}}{C}{=}OAlCl_3$$

$$C_6H_5\overset{\underset{|}{CH_3}}{C}{=}OAlCl_3 + Br_2 \xrightarrow{AlCl_3} 3\text{-}BrC_6H_4\overset{\underset{|}{CH_3}}{C}{=}OAlCl_3 + HBr$$

$$3\text{-}BrC_6H_4\overset{\underset{|}{CH_3}}{C}{=}OAlCl_3 \xrightarrow[H^+]{H_2O} 3\text{-}BrC_6H_4\overset{\underset{|}{CH_3}}{C}{=}O + Al^{3+} + 3Cl^-$$

Submitted by D. E. Pearson, H. W. Pope, and W. W. Hargrove.[1]
Checked by B. C. McKusick and D. W. Wiley.

1. Procedure

The apparatus consists of a 1-l. three-necked flask equipped with a condenser, a dropping funnel, and a stirrer terminating in a stiff, crescent-shaped Teflon polytetrafluoroethylene paddle. The stirrer motor must have good torque (Note 1). The assembled apparatus, which is protected from moisture by means of drying tubes in the condenser and funnel, is preferably predried. About 216-224 g. (1.62–1.68 moles) of powdered anhydrous aluminum chloride is added to the apparatus with as little exposure to the moisture of the air as possible (Note 2). While

the free-flowing catalyst is stirred (Note 3), 81 g. (0.67 mole) of acetophenone is added from the dropping funnel in a slow stream over a period of 20–30 minutes. Considerable heat is evolved, and, if the drops of ketone are not dispersed, darkening or charring occurs. When about one-third of the acetophenone has been added, the mixture becomes a viscous ball-like mass that is difficult to stir. Turning of the stirrer by hand or more rapid addition of ketone is necessary at this point. The addition of ketone, however, should not be so rapid as to produce a temperature above 180°. Near the end of the addition, the mass becomes molten and can be stirred easily without being either heated or cooled. The molten mass, in which the acetophenone is complexed with aluminum chloride, ranges in color from tan to brown.

Bromine (128 g., 0.80 mole) is added dropwise to the well-stirred mixture over a period of 40 minutes (Note 4). After all the bromine has been added, the molten mixture is stirred at 80–85° on a steam bath for 1 hour, or until it solidifies if that happens first (Note 5). The complex is added in portions to a well-stirred mixture of 1.3 l. of cracked ice and 100 ml. of concentrated hydrochloric acid in a 2-l. beaker (Note 6). Part of the cold aqueous layer is added to the reaction flask to decompose whatever part of the reaction mixture remains there, and the resulting mixture is added to the beaker. The dark oil that settles out is extracted from the mixture with four 150-ml. portions of ether. The extracts are combined, washed consecutively with 100 ml. of water and 100 ml. of 5% aqueous sodium bicarbonate solution, dried with anhydrous sodium sulfate, and transferred to a short-necked distillation flask. The ether is removed by distillation at atmospheric pressure, and crude 3-bromoacetophenone is stripped from a few grams of heavy dark residue by distillation at reduced pressure. The colorless distillate is carefully fractionated in a column 20 cm. long and 1.5 cm. in diameter that is filled with Carborundum or Heli-Pak filling. The combined middle fractions of constant refractive index are taken as 3-bromoacetophenone; weight, 94-100 g. (70-75%); b.p. 75 76°/0.5 mm.; n_D^{25} 1.5738 1.5742; m.p. 7 8° (Notes 7 and 8).

2. Notes

1. Among satisfactory motors are the Sargent Cone Drive and the Waco.

2. Exposure of the aluminum chloride to air is conveniently avoided by introducing the entire contents of two 4-ounce bottles of anhydrous resublimed aluminum chloride of the Baker and Adamson Company directly into the reaction flask.

3. If the paddle width is so small as to leave isolated, unagitated portions of aluminum chloride, it should be moved near the surface to disperse the ketone rapidly. If the ketone is not dispersed, condensation to dypnone occurs. Tars found in the stripping process are believed to originate from improper addition of the ketone to the aluminum chloride.

4. The rate of addition is regulated by the rate of evolution of hydrogen bromide. The yield of product is essentially the same whether the reaction mixture is held at 80–85° or at room temperature.

5. If the reaction mixture does not solidify during the heating, it is well to work it up at once while it can still be poured from the flask. Otherwise the work-up can be postponed to the next day. If the reaction mixture is too difficult to remove from the flask, the acid-ice slurry can be added *all at once* to the reaction flask immersed in ice. The vigorous surface decomposition is thus partly quenched. However, the cake is seldom difficult to remove unless polyhalogenation has occurred.

6. The acid prevents the formation of insoluble aluminum salts that make separation of ether-water layers difficult. It is helpful in this regard to stir the mixture of water, ketone, and acid for an hour or so before extracting the ketone with ether.

7. The present procedure has been used by the submitters to prepare the following 3-bromoacetophenones and benzaldehydes in the indicated yields:[2] 3-bromopropiophenone, m.p. 40–41°, 60%; 3-bromo-4-methylacetophenone, m.p. 42–43°, 56%; 3,4-dibromoacetophenone, m.p. 89–90°, 55%; 3-bromo-4-*tert*-butylacetophenone, b.p. 92°/0.1 mm., 30%; 3,5-dibromo-4-methylacetophenone, m.p. 102–103°, 57%; 3-bromobenzaldehyde, b.p. 105-106°/2 mm., 59%; 3-bromo-4-tolualdehyde, m.p. 48-49°, 44%.

8. The same procedure can be used to prepare 3-chloroaceto-phenones and benzaldehydes. The apparatus is modified by replacing the dropping funnel with a gas-inlet tube that permits chlorine to be introduced under the surface of the molten complex of acetophenone and aluminum chloride. For a run with 81 g. (0.67 mole) of acetophenone, 31 ml. (48 g., 0.67 mole) of liquid chlorine is condensed in a trap cooled with solid carbon dioxide and acetone. The gas is passed consecutively through a safety trap, a bubble counter containing concentrated sulfuric acid, and the inlet tube into the stirred complex. The rate of addition is controlled by gradually lowering the cooling bath surrounding the liquid chlorine trap. The internal temperature of the reaction mixture rises just above room temperature and the color of the complex changes from light brown to deep red-brown. The addition of chlorine is complete in 10–14 hours; with a faster rate of addition, some chlorine escapes. Stirring is continued for another hour, and the reaction mixture is worked up. The submitters have prepared the following in this way:[2] 3-chloroacetophenone, b.p. 61–63°/0.5 mm., 54%; 3-chlorobenz-aldehyde, b.p. 93–96°/15 mm., 43%; 2,3,5,6-tetrachloro-4-methylacetophenone, m.p. 98.5–99.5°, 67%.

3. Methods of Preparation

Nuclear halogenation of acetophenone depends on formation of the aluminum chloride complex. If less than one equivalent of aluminum chloride is used, side-chain halogenation occurs.[3] 3-Bromoacetophenone has been prepared from 3-aminoaceto-phenone by the Sandmeyer reaction.[4,5] The synthesis described here has been taken from work of the submitters,[2] who have used it to prepare many 3-bromo- and 3-chloroacetophenones and benzaldehydes, as well as more highly halogenated ones (Notes 7 and 8).

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

[2] D. E. Pearson, H. W. Pope, W. W. Hargrove, and W. E. Stamper, *J. Org. Chem.*, **23**, 1412 (1958).
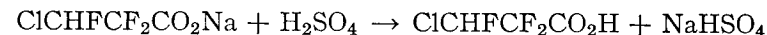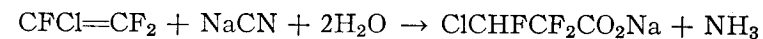
[3] R. M. Cowper and L. H. Davidson, *Org. Syntheses*, Coll. Vol. 2, 480 (1943).

[4] L. A. Elson, C. S. Gibson, and J. D. A. Johnson, *J. Chem. Soc.*, **1930**, 1128.

[5] C. S. Marvel, R. E. Allen, and C. G. Overberger, *J. Am. Chem. Soc.*, **68**, 1089 (1946).

3-CHLORO-2,2,3-TRIFLUOROPROPIONIC ACID

(Propionic acid, 3-chloro-2,2,3-trifluoro-)

$$CFCl{=}CF_2 + NaCN + 2H_2O \rightarrow ClCHFCF_2CO_2Na + NH_3$$
$$ClCHFCF_2CO_2Na + H_2SO_4 \rightarrow ClCHFCF_2CO_2H + NaHSO_4$$

Submitted by D. C. England and L. R. Melby.[1]
Checked by Max Tishler and W. J. Jones.

1. Procedure

Caution! This is a strongly exothermic reaction. The reaction should be carried out in a hood. A protective shield should be placed between the operator and the reaction bottle.

A modified Parr low-pressure hydrogenation apparatus is used for this preparation.[2] The bottle is fitted with a two-holed rubber stopper through which is passed a thermocouple well made of 5-mm. glass tubing and a gooseneck made of 8-mm. heavy-walled glass tubing. The thermocouple well extends into the bottle within about 2 cm. of the bottom. The gooseneck extends 1 cm. into the bottle, and the other end is connected directly to a manifold system with heavy-walled pressure tubing using screw clamps. Also attached to the manifold system through needle valves are a vacuum line, a storage cylinder of chlorotrifluoroethylene, a pressure gauge, and a bleed line.

The bottle is charged with 52 g. (1.0 mole) of 95% sodium cyanide, 100 ml. of water, and 100 ml. of acetonitrile, giving a two-phase liquid system. After the bottle is clamped in the metal cage of the shaking apparatus, the bottle is evacuated and filled to a gauge pressure of 10 lb. (0.68 atm.) with chlorotrifluoro-ethylene. This procedure is repeated twice to purge the system of air. Finally, the bottle is pressured to 40 lb. (2.7 atm.), chloro-trifluoroethylene leaving the valve open to maintain this pressure (Note 1). The thermocouple is fitted into place and shaking is started. The temperature steadily increases, and in 10–15 minutes it is about 75° and rising more rapidly. It is kept at 75–80° by cooling and/or slowing the rate of chlorotrifluoroethylene addition. *Caution! Careful control of the reaction is mandatory.*

If the reaction rate cannot be controlled, it is imperative to shut the gas addition valve and to stop the agitation immediately. Cooling is accomplished by packing ice inside the wire cage holding the bottle and/or pouring ice water on the bottle. When cooling is used, it is possible to complete the reaction in 1 hour. When the rate of chlorotrifluoroethylene absorption is negligible and the temperature is about 30°, pressure is released through the bleed line and the bottle is removed. The gain in weight is 130–135 g. (about 1.1 moles).

The product is a dark-colored solution which is poured slowly into sulfuric acid (100 ml. of concentrated sulfuric acid in 100 ml. of water) with cooling (Note 2). *This operation should be conducted in a hood because some hydrogen cyanide may be evolved from unreacted sodium cyanide.* The mixture is then extracted four times with 100-ml. portions of ether (Note 3). The first 100 ml. of ether yields about 260 ml. of organic material, and succeeding portions about 95 ml. each. The extract is dried over about 20 g. of magnesium sulfate and distilled (Note 4). After removal of low-boiling materials, there is obtained 124–128 g. (76–79%) of crude 3-chloro-2,2,3-trifluoropropionic acid, b.p. 70–85°/30 mm.; the bulk of this fraction distills at 83°/30 mm., n_D^{25} 1.3708–1.3717. This product is of sufficient purity for most purposes (Note 5). About 25–30 g. of high-boiling residue remains which is chiefly chlorotrifluoropropionamide (Note 6).

2. Notes

1. The chlorotrifluoroethylene cylinder is fitted with a pressure-reduction valve which is set at a maximum pressure of 40 lb. (2.7 atm.).

2. The amount of product was not changed by cooling, but the acidification reaction is very exothermic and cooling is necessary before extraction with ether.

3. The checkers encountered troublesome emulsions in the extraction step. It was found helpful to filter the acidified reaction mixture through a sintered-glass funnel before ether extraction.

4. A precision distillation column is not necessary. The submitters have used an 80-cm. spinning-band column with a 10 mm.

inside diameter or a 25-cm. helix-packed column of about 10 mm. inside diameter.

5. The neutral equivalent of this material is 169–173 (theory is 162.5). It is readily purified by mixing it thoroughly with 10% of its weight of phosphorus pentoxide and redistilling. The purified acid boils at 82–83°/30 mm. (159–160°/760 mm.), n_D^{25} 1.3695, N.E. 163.5. Recovery from the crude is 92%.

6. The higher-boiling material is largely 3-chloro-2,2,3-trifluoropropionamide, and some fractions crystallize at room temperature. The amide can be purified by redistillation, b.p. 111–112°/30 mm. (198–200°/760 mm.) or recrystallization from carbon tetrachloride. The pure amide melts at 41–42°. The amount of amide formed is not changed by running the above charge at a lower temperature. However, when the amount of water is reduced to 50 ml. and the temperature kept below 50°, the yield of crude acid is 38% and of amide, 21%. When the same charge is run at 80° maximum temperature, the yield of crude acid is 78% and of amide, 7%.

3. Methods of Preparation

3-Chloro-2,2,3-trifluoropropionic acid has been prepared by permanganate oxidation of 3-chloro-2,2,3-trifluoropropanol [3] which is one of the telomerization products of chlorotrifluoroethylene with methanol. The present procedure is a modification of one reported earlier [4] and is undoubtedly the method of choice for making propionic acids containing 2–4 fluorine atoms, i.e., 2,2,3,3-tetrafluoropropionic acid, 3,3-dichloro-2,2-difluoropropionic acid, and 3-bromo-2,2,3-trifluoropropionic acid. When preparing 2,2,3,3-tetrafluoropropionic acid from tetrafluoroethylene, it is desirable to use an additional 50 ml. of acetonitrile and externally applied heat to initiate the reaction.

[1] Contribution No. 554 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company.

[2] R. Adams and V. Voorhees, *Org. Syntheses*, Coll. Vol. **1**, 66 (Fig. 6) (1941). Later models of this apparatus use a larger-mouthed bottle which is more easily adapted to this preparation.

[3] R. M. Joyce, U. S. pat. 2,559,628 (1951) [*C. A.*, **46**, 3063 (1952)].

[4] D. C. England, L. R. Melby, and R. V. Lindsey, Jr., *J. Am. Chem. Soc.*, **80**, 6442 (1958).

2-CYCLOHEXENONE
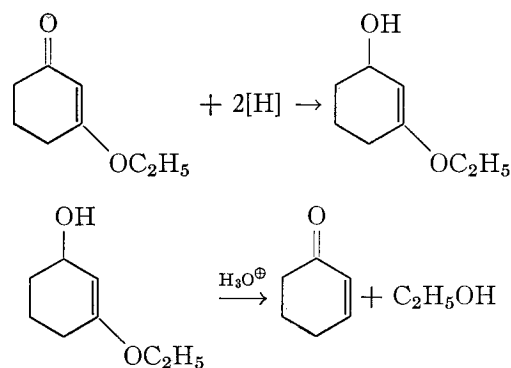
Submitted by Walter F. Gannon and Herbert O. House.[1]
Checked by William E. Parham, Allan M. Huffman,
George J. Meisters, and Wayland E. Noland.

1. Procedure

In a dry 500-ml. three-necked flask, equipped with a reflux condenser, a mechanical stirrer, and a dropping funnel and protected from atmospheric moisture with drying tubes, are placed 6.0 g. (0.16 mole) of lithium aluminum hydride and 200 ml. of anhydrous ether. A solution of 43 g. (0.307 mole) of 3-ethoxy-2-cyclohexenone (Note 1) in 50 ml. of anhydrous ether is added, dropwise and with stirring, to the reaction flask at a rate which maintains gentle refluxing of the solvent (Note 2). After the addition is complete, the reaction solution is boiled under reflux for an additional 30 minutes and then allowed to cool. The complex is hydrolyzed and the excess lithium aluminum hydride is destroyed by the cautious addition, dropwise and with stirring, of 15 ml. of water (Note 3). The resulting reaction mixture is poured into 500 ml. of cold aqueous 10% sulfuric acid. The ether layer which forms is separated, and the residual aqueous phase is extracted with three 300-ml. portions of ether. The combined ether solutions are washed successively with one 100-ml. portion of water and one 100-ml. portion of saturated, aqueous sodium bicarbonate solution and then dried over magnesium sulfate. The ether is removed by distillation through a 50-cm. Vigreux column,

and the residue is distilled under reduced pressure through a 40-cm. spinning-band column (Note 4). The yield of 2-cyclohexenone (Note 5), b.p. 56–57.5°/10 mm. or 96–97°/72 mm., n_D^{27} 1.4858, is 18.2–22.1 g. (62–75%).

2. Notes

1. The preparation of 3-ethoxy-2-cyclohexenone is described elsewhere in this volume.[2]
2. This addition requires approximately 1.5 hours.
3. The addition of water is accompanied by foaming, and care must be taken to avoid excessive loss of the solvent.
4. The 2-cyclohexenone obtained by an ordinary distillation at this point is contaminated with lower-boiling impurities (see Note 5), primarily ether and ethanol.
5. The purity of the 2-cyclohexenone may be assayed by gas chromatography on an 8 mm. x 215 cm. column heated to 125° and packed with di-(2-ethylhexyl) sebacate suspended on ground firebrick. This method of analysis indicates that the 3-cyclohexenone in the product amounts to no more than 3%. The fore-run from this fractional distillation contains substantial amounts of 2-cyclohexenone accompanied by ether, ethanol, and minor amounts of other lower-boiling impurities. Additional quantities of pure 2-cyclohexenone can be recovered by redistillation of this fore-run. The preparation of 2-cyclohexenone has been run on twice the scale described with no loss in yield. The ultraviolet spectrum of an ethanol solution of the 2-cyclohexenone obtained has a maximum at 226 mμ (ϵ = 10,400).

3. Methods of Preparation

2-Cyclohexenone has been prepared by dehydrohalogenation of 2-bromocyclohexanone,[3,4] by the hydrolysis and oxidation of 3-chlorocyclohexene,[5] by the dehydration of α-hydroxycyclohexanone,[6] by the oxidation of cyclohexene with chromic acid[7] or hydrogen peroxide in the presence of a vanadium catalyst,[8] by the addition of acrolein to ethyl acetoacetate followed by cyclization, hydrolysis, and decarboxylation,[9] by the reduction of N,N-dimethylaniline with sodium and ethanol in liquid ammonia

followed by hydrolysis,[10] by the reduction of anisole with lithium in liquid ammonia,[11] and by the reduction of 3-alkoxy-2-cyclohexanones with lithium aluminum hydride followed by acid-catalyzed hydrolysis and dehydration.[12]

The procedure described illustrates a general method for the preparation of α,β-unsaturated aldehydes and ketones from the enol ethers of β-dicarbonyl compounds.[12–14]

[1] Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts.

[2] See p. 41, this volume.

[3] E. A. Braude and E. A. Evans, *J. Chem. Soc.*, **1954**, 607.

[4] I. N. Nazarov, L. D. Bergel'son, I. V. Torgov, and S. N. Ananchenko, *Izvest. Akad. Nauk S. S. S. R., Otdel. Khim. Nauk*, **1953**, 889; *C.A.*, **49**, 1082 (1955).

[5] C. Courtot and J. Pierron, *Bull. soc. chim. France*, **45** (4), 286 (1929).

[6] P. D. Bartlett and G. F. Woods, *J. Am. Chem. Soc.*, **62**, 2933 (1940).

[7] F. C. Whitmore and G. W. Pedlow, Jr., *J. Am. Chem. Soc.*, **63**, 758 (1941).

[8] W. Treibs, G. Franke, G. Leichsenring, and H. Roder, *Ber.*, **86**, 616 (1953).

[9] M. Mousseron, R. Jacquier, A. Fontaine, and R. Zagdoun, *Bull. soc. chim. France*, **1954**, 1246.

[10] A. J. Birch, *J. Chem. Soc.*, **1946**, 593.

[11] A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, **75**, 5360 (1953).

[12] H. Born, R. Pappo, and J. Szmuszkovicz, *J. Chem. Soc.*, **1953**, 1779.

[13] P. Seifert and H. Schinz, *Helv. Chim. Acta*, **34**, 728 (1951).

[14] H. Favre, B. Marinier, and J. C. Richer, *Can. J. Chem.*, **34**, 1329 (1956).

DEOXYANISOIN

[Acetophenone, 4′-methoxy-2-(*p*-methoxyphenyl)-]

$$CH_3O-\langle\phi\rangle-CHOH-CO-\langle\phi\rangle-OCH_3 + Sn + 2HCl \rightarrow$$

$$CH_3O-\langle\phi\rangle-CH_2CO-\langle\phi\rangle-OCH_3 + SnCl_2 + H_2O$$
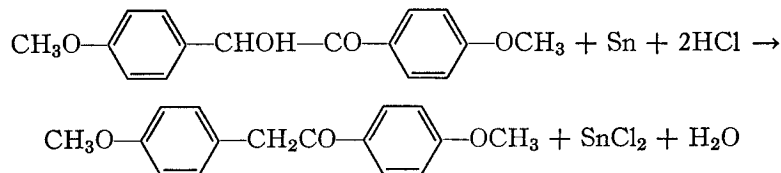
Submitted by P. H. CARTER, J. CYMERMAN CRAIG, RUTH E. LACK, and M. MOYLE.[1]
Checked by MAX TISHLER and E. M. CHAMBERLIN.

1. Procedure

A 500-ml. round-bottomed flask, equipped with a reflux condenser, is charged with 40 g. (0.33 mole) of powdered tin (Notes

1 and 2), 52 g. (0.19 mole) of anisoin (Note 3), 52 ml. of concentrated hydrochloric acid (Note 4), and 60 ml. of 95% alcohol. After the mixture is refluxed for 24 hours (Note 5), the boiling solution is decanted from undissolved tin, cooled to 0°, and the white crystals are filtered by suction. The filtrate is heated to boiling and then used to wash the tin by decantation. The combined washings are cooled to 0°, and the crystalline solid is collected by suction filtration. Recrystallization of the combined solids from 450 ml. of boiling 95% ethanol (Notes 6 and 7) gives, on cooling to 0°, colorless crystals of deoxyanisoin melting at 108–111°. The yield is 42–45 g. (86–92%).

2. Notes

1. A reduction in the amount of tin lowers the yield. Best results are obtained using powdered tin of between 100 and 200 mesh size. Use of tin coarser than 100 mesh results in the presence of unchanged anisoin, while tin finer than 200 mesh tends to conglomerate, causing lower yields. The checkers used tin obtained from E. H. Sargent Co., Chicago, labeled 200 mesh.

2. No advantage is gained by using amalgamated tin.

3. This procedure is generally applicable to the preparation of symmetrical deoxybenzoins. The submitters have prepared (*a*) deoxybenzoin (m.p. 56–58°) in 80–84% yield from 53 g. of benzoin (0.25 mole), 53 ml. of concentrated hydrochloric acid, 50 ml. of 95% alcohol, and 53 g. of powdered tin (0.44 mole), recrystallizing from 160 ml. of boiling 95% alcohol and cooling to 0°; (*b*) deoxypiperoin (m.p. and mixed m.p. 112–114°) in 89% yield from 14.3 g. of piperoin (0.048 mole), 13 ml. of concentrated hydrochloric acid, 30 ml. of 95% alcohol, and 10 g. of powdered tin (0.083 mole), recrystallizing from 140 ml. of boiling 95% alcohol and cooling to 0°.

4. A reduction in the amount of hydrochloric acid lowers the yield.

5. Lower yields are obtained by using reflux periods of 16 or 18 hours.

6. The checkers recommend washing the product with cold 95% alcohol; otherwise the product tends to discolor on standing.

7. Addition of water to the filtrate does not yield any further crystalline products.

3. Methods of Preparation

The synthesis of deoxybenzoin from phenacetyl chloride and benzene by the Friedel-Crafts reaction has been described.[2] For symmetrically substituted deoxybenzoins, direct reduction of the readily accessible benzoin is a more convenient method. Reduction of benzoin by zinc dust and acetic acid,[3] and by hydrochloric acid and granulated tin [4,5] or amalgamated powdered tin [6] has been reported. The present method is based on a publication of the authors.[7]

[1] Dyson Perrins Laboratory, Oxford, England.

[2] C. F. H. Allen and W. E. Barker, *Org. Syntheses*, Coll. Vol. **2**, 156 (1943).

[3] E. P. Kohler and E. M. Nygaard, *J. Am. Chem. Soc.*, **52**, 4133 (1930).

[4] J. S. Buck and S. S. Jenkins, *J. Am. Chem. Soc.*, **51**, 2163 (1929).

[5] I. Allen and J. S. Buck, *J. Am. Chem. Soc.*, **52**, 310 (1930).

[6] O. A. Ballard and W. M. Dehn, *J. Am. Chem. Soc.*, **54**, 3970 (1932).

[7] P. H. Carter, J. C. Craig, R. E. Lack, and M. Moyle, *J. Chem. Soc.*, **1959**, 476.

4,4'-DIAMINOAZOBENZENE

(Aniline, 4,4'-azodi-)
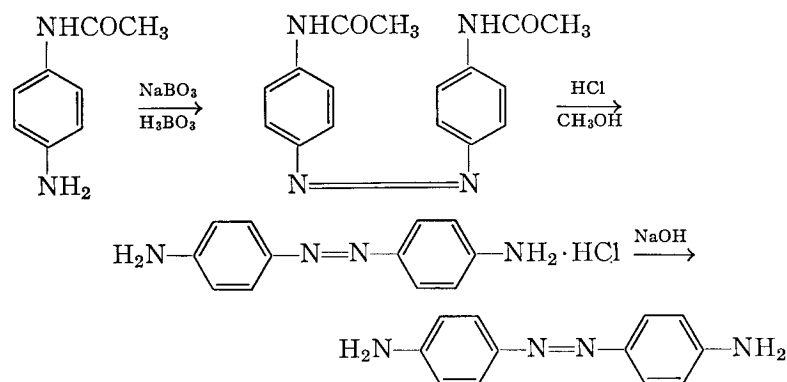
Submitted by Pasco Santurri, Frederick Robbins, and Robert Stubbings.[1]

Checked by Max Tishler, Earl M. Chamberlin, and William Harrison.

1. Procedure

In a 1-l. three-necked round-bottomed flask equipped with an efficient stirrer, a reflux condenser, and a thermometer (Note 1) are placed 500 ml. of glacial acetic acid (Note 2), 29.0 g. (0.19 mole) of *p*-aminoacetanilide (Note 3), 40 g. (0.26 mole) of sodium perborate tetrahydrate, and 10 g. (0.16 mole) of boric acid. The mixture is heated with stirring to 50–60° and held at this temperature for 6 hours. Initially the solids dissolve but, after heating for approximately 40 minutes, the product begins to separate. At the end of the reaction period, the mixture is cooled to room temperature and the yellow product is collected on a Büchner funnel. It is washed with water until the washings are neutral to pH paper (Note 4) and then dried in an oven at 110°. The yield of 4,4'-bis(acetamido)azobenzene, m.p. 288–293° (dec.), is 16.5 g. (57.7%). It is used as such for the hydrolysis step (Note 5).

In a 500-ml. round-bottomed flask equipped with a reflux condenser and a magnetic stirrer (Note 6) are placed 150 ml. of methanol, 150 ml. of 6N hydrochloric acid, and the total yield of 4,4'-bis(acetamido)azobenzene. The mixture is heated under reflux for 1.5 hours. The reaction mixture is cooled and the violet solid collected on a Büchner funnel (Note 7). The damp product is suspended in 500 ml. of water in a 1-l. beaker equipped with a stirrer, and the mixture is slowly neutralized by the addition of 2.5N sodium hydroxide. In the course of the neutralization, the salt dissolves and the free base separates. The 4,4'-diaminoazobenzene is collected on a Büchner funnel, washed with water, and dried under reduced pressure. The yield of yellow product, m.p. 238–241° (dec.), is 11–12 g. The over-all yield from *p*-aminoacetanilide is 52–56%.

2. Notes

1. The submitters carried out the reaction in a 1-l. beaker. The checkers found that considerable evaporation of acetic acid occurs when a beaker is used.

2. The use of dilute acetic acid decreases the yield.

3. Technical grade *p*-aminoacetanilide (m.p. 158–160°) obtained from Eastman Kodak Company (T-13) was used.

4. If the product is not washed well, the dried material will turn violet, indicating unreacted *p*-aminoacetanilide.

5. Witt and Kopetschni[2] report a melting point of 295–296° (dec.). This compound may be recrystallized from glacial acetic acid or ethanol.

6. The submitters did not stir the hydrolysis mixture. The checkers found that, if stirring was omitted, bumping occurred during the reflux period.

7. This product is probably the monohydrochloride salt. The dihydrochloride is reported to be red.[3]

3. Methods of Preparation

4,4′-Diaminoazobenzene was reported by Nietzki[4] to have been prepared by diazotizing *p*-nitroaniline and coupling the product with aniline. The resulting 4-nitrodiazoaminobenzene[5] is rearranged and the nitro group reduced. The submitters tried several times to carry out this procedure but were unsuccessful. 4,4′-Diaminoazobenzene has been prepared by the oxidation of *p*-nitroaniline with potassium persulfate[6] followed by the reduction of the nitro groups.[7]

The general method used by the submitters has been reported by others[8] for the preparation of other azo compounds.

4. Use of 4,4′-Diaminoazobenzene

The product is useful as a model compound for studies of the chemistry of derivatives of colored diamines. Specifically, the submitters used the compound for the preparation of colored diisocyanates.

[1] Leather Research Institute, Lehigh University, Bethlehem, Pennsylvania.
[2] O. N. Witt and E. Kopetschni, *Ber.*, **45**, 1134 (1912).
[3] F. Kehrmann and S. Hempel, *Ber.*, **50**, 867 (1917).
[4] R. Nietzki, *Ber.*, **17**, 343 (1884).
[5] E. Noelting and F. Binder, *Ber.*, **20**, 3015 (1887).
[6] A. H. Cook and D. G. Jones, *J. Chem. Soc.*, **1939**, 1309.
[7] J. N. Ashley, H. J. Barber, A. J. Ewins, G. Newbery, and A. D. H. Self, *J. Chem. Soc.*, **1942**, 103.
[8] S. M. Mehta and M. V. Vakilwala, *J. Am. Chem. Soc.*, **74**, 563 (1952).

DIETHYL ACETAMIDOMALONATE

(Malonic acid, acetamido-, diethyl ester)

$$CH_2(CO_2C_2H_5)_2 + NaNO_2 + CH_3CO_2H \rightarrow$$
$$HON{=}C(CO_2C_2H_5)_2 + CH_3CO_2Na + H_2O$$

$$HON{=}C(CO_2C_2H_5)_2 + 2Zn + 3CH_3CO_2H + (CH_3CO)_2O \rightarrow$$
$$CH_3CONHCH(CO_2C_2H_5)_2 + 2Zn(C_2H_3O_2)_2 + H_2O$$
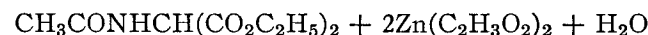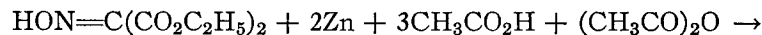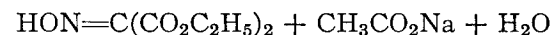
Submitted by Arthur J. Zambito and Eugene E. Howe.[1]
Checked by John C. Sheehan and Alma M. Boston.

1. Procedure

A. *Diethyl isonitrosomalonate.* In a 500-ml. three-necked, round-bottomed flask, equipped with a mechanical stirrer and thermometer, is placed 50 g. (47.4 ml., 0.312 mole) of diethyl malonate. The flask is cooled in an ice bath, and a mixture of glacial acetic acid and 81 ml. of water is added with stirring. With the temperature at about 5°, a total of 65 g. of sodium nitrite (Note 1) (0.944 mole) is added in portions over a period of 1.5 hours, the temperature being maintained around 5° during the addition. After all the sodium nitrite is added, the ice bath is removed, and the stirring is continued for 4 hours (Note 2). During this time, the temperature reaches a maximum of 34–38° within 2 hours and falls to about 29° by the end of the stirring period. Gases which escape during the reaction (mostly oxides of nitrogen) are led to the hood.

The reaction mixture is transferred to a 300-ml. separatory funnel and is extracted with two 50-ml. portions of ether. The combined ethereal solution of diethyl isonitrosomalonate is used in the next step immediately or, if desired, may be used after storage in a refrigerator overnight (Note 3).

B. *Diethyl acetamidomalonate.* The solution of diethyl iso-

nitrosomalonate described above, 86 g. (0.842 mole) of acetic anhydride, and 225 ml. (3.95 moles) of glacial acetic acid are placed in a 1-l., three-necked, round-bottomed flask fitted with a mechanical stirrer, a thermometer, and a dropping funnel. With vigorous stirring 78.5 g. (1.20 moles) of zinc dust is added in small portions over a period of 1.5 hours in such a manner that the temperature of the reaction is maintained at 40–50°. The reaction is markedly exothermic during most of the zinc addition, and intermittent cooling (water bath) is required. After all the metal has been added, the mixture is stirred for an additional 30 minutes.

The reaction mixture is filtered with suction and the cake is washed thoroughly with two 200-ml. portions of glacial acetic acid (Note 4). The combined filtrate and washings are evaporated under reduced pressure on the steam bath until a thick oil, which generally partially crystallizes, remains. To purify the crude product, 100 ml. of water is added, and the flask is warmed on a steam bath until the solid melts. The mixture of water and oil is stirred rapidly in an ice bath, and diethyl acetamidomalonate crystallizes as a fine white product. After cooling in an ice bath for an additional hour, the product is collected by filtration, washed once with cold water, and dried in air at 50°. A second crop is obtained by concentrating the mother liquor under reduced pressure. The yield of diethyl acetamidomalonate, m.p. 95–97° (Note 5), is 52–53 g. (77–78%) based on malonic ester.

2. Notes

1. Owing to the instability of sodium nitrite solutions, the addition of the solid salt is preferred.

2. Prolonging the stirring to 24 hours has no effect on the yield of diethyl acetamidomalonate.

3. No attempt has been made to purify diethyl isonitrosomalonate. This product has been known to explode during distillation.

4. The zinc cake is very heavy and may be washed by slurrying on a sintered-glass funnel or, if a standard Büchner funnel is used, by removing and slurrying in a beaker.

5. The diethyl acetamidomalonate obtained is of high purity. If a product of inferior quality is obtained, it may be recrystallized from hot water, using 2.5 cc. per g. Upon cooling, the product separates first as an oil. With rapid stirring, it is converted to fine white crystals which are easily washed with cold water. Diethyl acetamidomalonate may be recrystallized in this manner with 97% recovery. The first crop amounts to 91% and the mother liquors may be concentrated to yield an additional 6%.

3. Methods of Preparation

Diethyl acetamidomalonate was first reported by Cherchez[2] in 1931, when in an attempt to carry out a carbon alkylation of diethyl aminomalonate with acetyl chloride he obtained a quantitative yield of diethyl acetamidomalonate. This method of preparation, however, is not practical since diethyl aminomalonate is unstable and is made in relatively poor yields.

Snyder and Smith[3] prepared diethyl acetamidomalonate in 40% yield by reduction of diethyl isonitrosomalonate in ethanol over palladium on charcoal followed by direct acetylation of diethyl aminomalonate in the filtrate with acetic anhydride. Ghosh and Dutta[4] used zinc dust instead of palladium. A modification using Raney nickel is described by Akabori et al.[5] Shaw and Nolan[6] reported a 98% yield by conversion of diethyl oximinomalonate-sodium acetate complex.

4. Use of Diethyl Acetamidomalonate

Diethyl acetamidomalonate is useful in the synthesis of α-amino acids by alkylation, as, for example, histidine and tryptophan.

[1] Merck Sharp and Dohme Research Laboratories, Division of Merck and Co., Rahway, New Jersey.
[2] V. Cherchez, *Bull. soc. chim.*, **49**, 45 (1931).
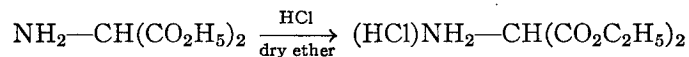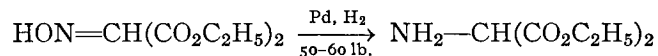[3] H. R. Snyder and C. W. Smith, *J. Am. Chem. Soc.*, **66**, 350 (1944).
[4] T. N. Ghosh and S. Dutta, *J. Indian Chem. Soc.*, **32**, 20 (1955).
[5] S. Akabori et al., Japan pat. 274 (January 20, 1954).
[6] K. N. F. Shaw and C. Nolan, *J. Org. Chem.*, **22**, 1668 (1957).

DIETHYL AMINOMALONATE HYDROCHLORIDE

(Malonic acid, amino-, diethyl ester, hydrochloride)

$$HON=CH(CO_2C_2H_5)_2 \xrightarrow[\text{50-60 lb.}]{\text{Pd, H}_2} NH_2-CH(CO_2C_2H_5)_2$$

$$NH_2-CH(CO_2H_5)_2 \xrightarrow[\text{dry ether}]{\text{HCl}} (HCl)NH_2-CH(CO_2C_2H_5)_2$$

Submitted by Walter H. Hartung, Jan H. R. Beaujon, and George Cocolas.[1]
Checked by John C. Sheehan and Robert W. Parsons, Jr.

1. Procedure

A. *Diethyl aminomalonate.* An ethereal solution (about 150 ml.) of diethyl isonitrosomalonate prepared from 50 g. of diethyl malonate (Note 1) is washed with 80-ml. portions of 1% sodium bicarbonate solution until the final washing has a distinct yellow color (Note 2). The ethereal solution is dried over 40 g. of anhydrous sodium sulfate in a refrigerator overnight and then filtered into a tared round-bottomed flask. The solvent is removed under reduced pressure at a temperature below 30° (water bath). The weight of the residue in one case was 59.6 g. Assuming complete conversion of the 0.312 mole of diethyl malonate to diethyl isonitrosomalonate, a 0.1-mole aliquot (19.1 g.) of the residue is placed in a 500-ml. reduction bottle provided for the Parr Hydrogenator (Note 3). To this is added 100 ml. of absolute alcohol and 3 g. of 10% palladium-on-charcoal catalyst (Note 4). The bottle is placed in a hydrogenator, and the system is flushed three or four times with hydrogen. With the initial reading on the pressure gauge at 50–60 lb., the bottle is shaken until no further drop in pressure is observed (about 15 minutes).

The catalyst is removed by filtration, using an absolute alcohol wash, and the clear filtrate is concentrated under reduced pressure at a temperature below 50° (water bath). As diethyl aminomalonate is not so stable as its salts, the crude product is con-verted directly to diethyl aminomalonate hydrochloride (Note 5).

B. *Diethyl aminomalonate hydrochloride.* The crude diethyl aminomalonate is diluted with 80 ml. of dry ether and filtered to remove a small amount of white solid. The filtrate is collected in a 250-ml. Erlenmeyer flask and cooled in an ice bath. Dry hydrogen chloride is passed just over the solution while it is being stirred mechanically (Note 6). The fine white crystals which precipitate are collected by suction filtration and washed three times with a total of 60 ml. of dry ether (Note 7). The filtrate and washings are treated again with hydrogen chloride, and a second crop of diethyl aminomalonate hydrochloride is collected and washed as before. This process is repeated until no further precipitation results from passing hydrogen chloride into the solution. A total of 16.5–17.4 g. (78–82% yield based on diethyl malonate) of diethyl aminomalonate hydrochloride, m.p. 162–163°, is obtained. Recrystallization from alcohol-ether affords a purer product, 164–165°.

2. Notes

1. It is convient to use the ether solution of diethyl isonitrosomalonate described by Zambito and Howe.[2]

2. About six washings are required. It may be necessary to add a total of 50 ml. of ether during the first three washings and 20 ml. during the final washing to facilitate breaking of the interphase emulsions. In each case, after partial separation of phases has occurred, ether is added and the separatory funnel is swirled gently until the interphase clears. The washing process requires about 1.5 hours.

3. As diethyl isonitrosomalonate may decompose with explosive violence on heating, further purification by distillation is not recommended.

According to the submitters, reductions using as much as 0.3 mole of diethyl isonitrosomalonate were carried out.

4. The checkers used 10% palladium-on-charcoal catalyst obtained from Baker and Company, Inc., 113 Astor Street, Newark, New Jersey.

5. According to the submitters, diethyl aminomalonate may be purified by distillation, b.p. 116–118°/12 mm. or 122–123°/16 mm.; $n_D^{16} = 1.4353$; $d_{14}^{16} = 1.100$.

6. Hydrogen chloride is dried by passage through a train of two gas washing bottles containing concentrated sulfuric acid. A 10-mm. tube through which the hydrogen chloride is passed is placed just over the stirring liquid, instead of under the surface, to prevent clogging of the tube by the bulky precipitate which is formed.

The checkers found magnetic stirring satisfactory. More ether may have to be added to prevent the heavy slurry from stopping the stirrer.

7. A medium-porosity sintered-glass funnel was used by the checkers.

3. Methods of Preparation

Diethyl isonitrosomalonate has been reduced catalytically, over palladium on charcoal,[3] Raney nickel,[4] and chemically by aluminium amalgam[5] or hydrogen sulfide.[6]

4. Use of Diethyl Aminomalonate Hydrochloride

Diethyl aminomalonate is a useful intermediate, lending itself to N-acylation;[3,7] the N-acyl derivatives may be alkylated by procedures as established for syntheses via malonic ester.

[1] Medical College of Virginia, Richmond, Virginia.

[2] See p. 21, this volume.

[3] H. R. Snyder and C. W. Smith, *J. Am. Chem. Soc.*, **66**, 350 (1944).

[4] C. E. Redemann and M. S. Dunn, *J. Biol. Chem.*, **130**, 341 (1939).

[5] R. Locquin and V. Cherchez, *Compt. rend.*, **186**, 1360 (1926).

[6] T. B. Johnson and B. H. Nicolet, *J. Am. Chem. Soc.*, **36**, 352 (1914).

[7] J. H. R. Beaujon and W. H. Hartung, *J. Am. Pharm. Assoc., Sci. Ed.*, **41**, 578 (1952); G. H. Cocolas and W. H. Hartung, *J. Am. Chem. Soc.*, **79**, 5203 (1957).

DIETHYL BIS(HYDROXYMETHYL)MALONATE

(Malonic acid, bis(hydroxymethyl)-, diethyl ester)

$$CH_2(CO_2C_2H_5)_2 + 2HCHO \rightarrow (HOHCH_2)_2C(CO_2C_2H_5)_2$$
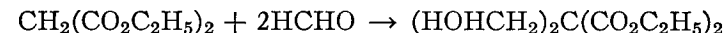
Submitted by PAUL BLOCK, JR.[1]
Checked by MELVIN S. NEWMAN and REINHARDT STEIN.

1. Procedure

Formaldehyde solution equivalent to 60 g. of formaldehyde (2 moles) (Note 1) and 8 g. of potassium bicarbonate (small crystals) are placed in an 800-ml. beaker standing in a water bath at 20° in a hood. Mechanical stirring is started and 160 g. (1 mole) of diethyl malonate (Note 2) is added dropwise during about 40–50 min., at such a rate that the temperature of the reaction mixture is held at 25–30°. Stirring is continued for 1 hour. The reaction mixture is transferred to a separatory funnel. A saturated solution of ammonium sulfate (320 ml.) (Note 3) is added and the mixture is extracted with 320 ml. of ether. The ethereal extract, dried for 1 hour with anhydrous sodium sulfate (20 g.), is filtered into a 1-l., three-necked flask through a fluted filter paper. The sodium sulfate and paper are washed with 50 ml. of anhydrous ether. The flask (fitted with a thermometer reaching to the bottom, a condenser set for downward distillation; third neck closed) is placed in a suitable heating bath (Note 4). Boiling chips are introduced and the ether is distilled until the temperature of the liquid has risen to 45–50°. The heating bath is then removed and the distillation assembly is replaced by a glass tube (about 4 mm. I.D.) reaching to the bottom of the flask and closed by a piece of rubber tubing and a screw clamp. An aspirator is now connected to the third neck of the flask. Vacuum is applied and volatile material is removed until the pressure falls to 20–30 mm. The temperature of the contents of the flask is brought to 40° and maintained there until crystallization begins and for an additional 30 minutes (Note 5). Isopropyl ether (500 ml.) (Note 6) is added. The mixture is warmed to 50° and swirled until the

product (crystalline and oily) dissolves. The solution is transferred to an Erlenmeyer flask, and cooled in ice water with stirring until a thick suspension of crystals results. The suspension is refrigerated for 1 hour, filtered with suction (rubber dam), and the crystals are dried overnight at room temperature, and then in a vacuum desiccator over sulfuric acid. The yield of colorless crystals, m.p. 48–50°, is 158–166 g. (72–75%). This product may be recrystallized from isopropyl ether (3.5 volumes) with an 85% recovery to yield material with m.p. 50–52°. Melting points of 52–53° and 52° are reported.[2,3]

2. Notes

1. Exactly 3 ml. of formaldehyde solution is assayed by the method of U.S.P. XIII, and the result calculated to grams of formaldehyde per milliliter of solution.

2. The diethyl malonate used boiled over a 2° range.

3. Ammonium sulfate (175 g.) is added to 235 ml. of water, warmed until it is dissolved, and cooled.

4. A heating mantle or liquid bath may be used.

5. The screw clamp may be adjusted so that there will be a spattering on the upper, cool part of the flask, while the pressure is still maintained below 30 mm. Under these conditions, the initiation of crystallization is speeded.

6. A practical grade is adequate, but it should be peroxide-free.

3. Methods of Preparation

The only reported method of preparation of diethyl bis(hydroxymethyl)malonate is by the reaction described here.[2,3]

4. Use of Diethyl Bis(hydroxymethyl)malonate

Diethyl bis(hydroxymethyl)malonate is a useful intermediate for preparing substituted malonic esters.

[1] *Toledo Blade*, Toledo, Ohio.

[2] K. N. Welch, *J. Chem. Soc.*, 1930, 257.

[3] H. Gault and A. Roesch, *Bull. soc. chim. France*, 5 (4), 1410 (1937).

2,5-DIMETHOXY-2,5-DIHYDROFURAN

(Furan, 2,5-dihydro-2,5-dimethoxy-)
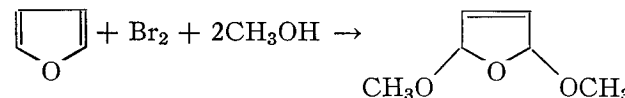
Submitted by D. M. Burness.[1]
Checked by Virgil Boekelheide and Roland P. F. Scharrer.

1. Procedure

In a 3-l., three-necked flask equipped with stirrer, thermometer, drying tube filled with soda-lime, and a dropping funnel are placed 155 ml. (146 g., 2.28 moles) of freshly distilled furan, 400 ml. of absolute ether, and 500 ml. of absolute methanol. The solution is cooled to −40° with a dry ice-acetone bath and a cold (−25°) solution of 112 ml. (320 g., 2.0 moles) of bromine in 1.3 l. of absolute methanol added during 10 minutes, the temperature being kept below −25°. After an additional 20-minute period, the dropping funnel is replaced with an open gas addition tube (Note 1) and ammonia gas is passed in at a moderate rate, with strong cooling to keep the temperature below −25° until the mixture is just basic to pH indicator paper (20–40 minutes). The solution is stirred at −25° for 1.5 hours and allowed to warm spontaneously to −5° (Note 2). The solution is again made slightly basic with ammonia and filtered, and the volatile solvents are removed by distillation at atmospheric pressure with stirring to minimize bumping. The ammonium bromide, which precipitates during the concentration, is then collected by filtration and the residual oil is distilled to give 187–197 g. (72–76%) (Note 3) of a clear oil (n_D^{25} 1.4327), boiling at 50–51° at 13 mm. (Note 4).

2. Notes

1. A sintered-glass tube has a tendency to clog.

2. The solution should now be colorless; otherwise stirring is continued until it becomes so.

3. This yield is based on the bromine used.

4. The submitters used a distillation column which was 5 in. long and packed with $3/16$-in. glass helices. Inclusion of a slightly higher-boiling fraction (b.p. 52–54°) brings the yield to 79–80%. Redistillation of the product is occasionally necessary if a yellow color develops, but the recovery is excellent.

3. Methods of Preparation

The 2,5-dialkoxy-2,5-dihydrofurans can be obtained by electrolytic oxidation of furan in alcoholic ammonium bromide [2] or by bromine oxidation of furan in the appropriate alcohol.[3,4]

4. Use of 2,5-Dimethoxy-2,5-dihydrofuran

The 2,5-dialkoxy-2,5-dihydrofurans are cyclic acetals of malealdehyde and may be used to generate this substance *in situ*. Also, the 2,5-dialkoxy-2,5-dihydrofurans readily undergo hydrogenation to provide the cyclic acetals of succindialdehyde.[4]

[1] Eastman Kodak Company, Rochester 4, New York.

[2] N. Clauson-Kaas, F. Limborg, and K. Glens, *Acta Chem. Scand.*, **6**, 531 (1952).

[3] N. Clauson-Kaas, F. Limborg, and J. Fakstorp, *Acta Chem. Scand.*, **2**, 109 (1948).

[4] J. Fakstorp, D. Raleigh, and L. E. Schniepp, *J. Am. Chem. Soc.*, **72**, 869 (1950).

N,N-DIMETHYLAMINOMETHYLFERROCENE METHIODIDE

{Iron, cyclopentadienyl[(dimethylaminomethyl)cyclopentadienyl]-, methiodide}
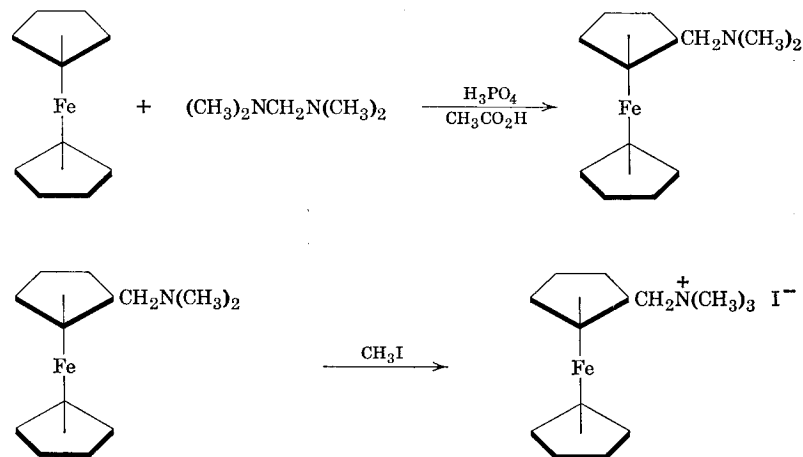
Submitted by Daniel Lednicer and Charles R. Hauser.[1]
Checked by B. C. McKusick, W. A. Sheppard, R. D. Vest, and H. F. Mower.

1. Procedure

Caution! Bis(dimethylamino)methane is a potent lachrymator, so it should be handled only in a hood.

Ferrocene (46.4 g., 0.250 mole) (Note 1) is added to a well-stirred solution of 43.2 g. (0.422 mole) of bis(dimethylamino)methane (Note 2) and 43.2 g. of phosphoric acid in 400 ml. of acetic acid in a 2-l. three-necked round-bottomed flask equipped with a condenser, a nitrogen inlet, and a mechanical stirrer (Note 3). The resulting suspension is heated on a steam bath under a slow stream of nitrogen (Note 4) for 5 hours (Note 5). The reaction mixture, a dark-amber solution, is allowed to cool to room temperature and is diluted with 550 ml. of water. The unreacted ferrocene is removed by extracting the solution with three 325-ml. portions of ether. The aqueous solution is then cooled in ice water and made alkaline by the addition of 245 g.

of sodium hydroxide pellets. The tertiary amine separates from the alkaline solution as an oil in the presence of some black tar (Note 6). The mixture is extracted with three 500-ml. portions of ether. The organic solution is washed with water and dried over sodium sulfate. Crude dimethylaminomethylferrocene is obtained as a dark-red mobile liquid when the solvent is removed at the water pump (Note 7).

To a gently swirled solution of the crude amine in 54 ml. of methanol is added 54 ml. (123 g., 0.87 mole) of methyl iodide. The solution is heated on a steam bath for 5 minutes and cooled to room temperature, and 800 ml. of ether is added. The methiodide, which separates as an oil, crystallizes on being scratched. The solid is collected on a Büchner funnel, washed with ether, and dried at 20–50 mm. for several hours at room temperature to yield 65–78 g. (68–81%; Note 8) of N,N-dimethylaminomethyl-ferrocene methiodide as an orange powder, m.p. 200° (dec.) (Note 9).

2. Notes

1. The ferrocene may be prepared by Wilkinson's procedures [2] or it may be purchased from Matheson, Coleman and Bell, East Rutherford, New Jersey, and other companies.

2. The amine, under the name N,N,N',N'-tetramethyl-methylenediamine, may be purchased from Ames Laboratories, South Norwalk, Connecticut. The checkers prepared it by the following procedure. A solution of 60.7 g. (0.75 mole) of 37% aqueous formaldehyde solution is placed in an 800-ml. beaker equipped with a mechanical stirrer and thermometer, and cooled in an ice bath. Two hundred seventy-one grams (1.50 moles) of a 25% aqueous solution of dimethylamine is added to this solution at a rate such that the reaction temperature is kept below 15°. The solution is stirred for 30 minutes after the addition is complete, and potassium hydroxide pellets (approximately 150 g.) are added in portions until the reaction mixture separates into two layers. The upper layer is separated, dried over potassium hydroxide pellets overnight, and distilled to give 59–64 g. (77–83%) of bis(dimethylamino)methane, b.p. 83–84°.[3]

3. The mixing of the amine and acids is exothermic. It is

necessary to add the amine dropwise to the solution of acids with stirring and cooling in an ice bath.

4. Since ferrocene and many of its derivatives are easily oxidized by air in the presence of acids, nitrogen is passed in at a rate sufficient to exclude air from the system.

5. It was found that the reaction is essentially complete after 5 hours. Further heating does not affect the yield.

6. The checkers found that the solution turned into a gel after the addition of sodium hydroxide. They obtained satisfactory results by adding 200 ml. of water to the gel, which made it fluid enough to be extractable with ether.

7. Distillation of the tertiary amine before methiodide formation does not significantly affect the yield or purity of the quaternary salt. The amine boils at 91–92°/0.45 mm.

8. The submitters report yields as high as 89%.

9. The melting point of this compound is ill-defined by reason of considerable darkening and shrinking that start at 175°. The product thus obtained is sufficiently pure for use in further reactions.[4]

3. Methods of Preparation

This procedure is based on the method of Lindsay and Hauser [3] as modified slightly by Osgerby and Pauson.[5] N,N-dimethyl-aminomethylferrocene methiodide has also been prepared by heating formylferrocene with dimethylamine and hydrogen in the presence of Raney nickel catalyst to give dimethylamino-methylferrocene, which was quaternized with methyl iodide.[6]

Essentially the present procedure converted 1-methylindole to 1-methyl-3-(N,N-dimethylaminomethyl)indole [7] and α-methyl-styrene to α-(N,N-dimethylaminoethyl)styrene.[8]

[1] Department of Chemistry, Duke University, Durham, North Carolina. The work was supported by the Office of Ordnance Research, U. S. Army.

[2] G. Wilkinson, *Org. Syntheses*, **36**, 31, 34 (1956).

[3] J. K. Lindsay and C. R. Hauser, *J. Org. Chem.*, **22**, 355 (1957).

[4] D. Lednicer, J. K. Lindsay, and C. R. Hauser, *J. Org. Chem.*, **23**, 653 (1958).

[5] J. M. Osgerby and P. L. Pauson, *J. Chem. Soc.*, **1958**, 656.

[6] P. J. Graham, K. V. Lindsey, G. W. Parshall, M. L. Peterson, and G. M. Whitman, *J. Am. Chem. Soc.*, **79**, 3416 (1957).

[7] H. R. Snyder and E. L. Eliel, *J. Am. Chem. Soc.*, **70**, 1703 (1948).

[8] G. F. Hennion, C. C. Price, and V. C. Wolff, Jr., *J. Am. Chem. Soc.*, **77**, 4633 (1955); C. J. Schmidle and R. C. Mansfield, *ibid.*, **77**, 4636 (1955).

2,4-DINITROIODOBENZENE

(Benzene, 1-iodo-2,4-dinitro-)
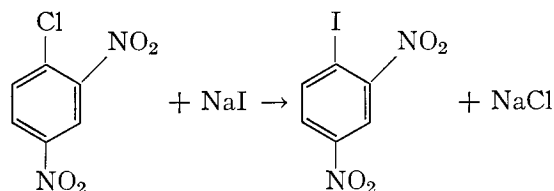
Submitted by J. F. Bunnett and R. M. Conner.[1]
Checked by Virgil Boekelheide and James S. Todd.

1. Procedure

Caution! 2,4-Dinitrochlorobenzene causes severe skin irritation to some individuals. Sensitive persons are advised to wear rubber gloves.

To 200 ml. of redistilled technical grade dimethylformamide (Note 1) in a 1-l. round-bottomed flask are added 150 g. (1 mole) of sodium iodide (Note 2) and 40.5 g. (0.2 mole) of 2,4-dinitro-chlorobenzene (Note 3). The flask is fitted with a reflux condenser, and the red-brown mixture is refluxed for 15 minutes over a free flame arranged to impinge somewhat off-center (Note 4).

The hot reaction mixture is poured with stirring over about 0.75 l. of crushed ice in a 2-l. beaker. The beaker is filled with water, and the mixture is stirred to dissolve inorganic salts (Note 5). The insoluble red-brown solid is collected on a suction filter. This crude product, even while damp, is transferred to a 2-l. round-bottomed flask, and 500 ml. of a mixture of 75% (375 ml.) of petroleum ether (b.p. 90–100°) and 25% (125 ml.) of benzene is added. The flask is provided with a reflux condenser, and the mixture is heated at reflux for 15 minutes by means of an electric mantle (Note 6). The resulting solution is decanted into a second 2-l. flask, leaving in the first flask some water and a red-brown solid residue. To the slightly cooled liquor in the

second flask is added cautiously 7 g. of powdered activated carbon. The carbon is dispersed by swirling, and the mixture is heated for an additional 5 minutes. The mixture is then filtered through a fluted filter into a 1-l. Erlenmeyer flask. This flask is stoppered and chilled to cause crystallization of the product (Note 7).

The product is collected on a suction filter. The yield of air-dried product, as yellow-orange crystals, m.p. 87–89°, is 38–42 g. (65–71%) (Note 8). A purer, lemon-yellow product, m.p. 88.5–90°, is obtained by an additional recrystallization from 1 l. of petroleum ether (b.p. 90–100°) with use of carbon; the yield after this second crystallization is 28–34 g. (48–58%).

2. Notes

1. Dimethylformamide is available from E. I. du Pont de Nemours and Co., Inc., Wilmington, Delaware.

2. Reagent grade sodium iodide was used.

3. Eastman Kodak white label 2,4-dinitrochlorobenzene, which had a light tan color, was used without further purification.

4. The burner should be so arranged that the flame impinges upon the side of the flask in such a way as to dissolve the sodium iodide from the top downward. The flask should be shaken or swirled frequently during the onset of boiling. A small amount of white solid remains undissolved even at reflux.

5. At this point there may be a lumpy, dark-brown material mixed with the orange-brown crude precipitated product. There appears to be no need to break up the lumps.

6. Alternatively, the flask can be heated on an efficient steam bath with swirling until the crude product melts. After an additional 15 minutes of heating, the solution can be decanted as described.

7. The submitters placed the flasks of warm filtrate in the refrigerator for storage overnight or in a freezing cabinet at −20° for at least 1 hour.

8. From a run of five times the scale described, the submitters obtained 219 g. (71%) of an orange-yellow crystalline product, m.p. 88–90°.

3. Methods of Preparation

2,4-Dinitroiodobenzene has been prepared by the nitration of o- or p-nitroiodobenzene,[2] by treatment of 2,4-dinitrobenzenediazonium sulfate with potassium iodide,[3] and by the reaction of sodium iodide with 2,4-dinitrochlorobenzene in refluxing ethylene glycol.[4] The present procedure is a modification [5] of the last-mentioned one.

[1] Department of Chemistry, University of North Carolina, Chapel Hill, North Carolina.

[2] W. Körner, *Gazz. chim. ital.*, **4**, 323 (1874).

[3] A. L. Beckwith, J. Miller, and G. D. Leahy, *J. Chem. Soc.*, **1952**, 3556.

[4] G. M. Bennett and I. H. Vernon, *J. Chem. Soc.*, **1938**, 1783.

[5] J. F. Bunnett and R. M. Conner, *J. Org. Chem.*, **23**, 305 (1958).

1,4-DIPHENYL-1,3-BUTADIENE

(1,3-Butadiene,1,4-diphenyl-)

$$C_6H_5CH{=}CHCH_2Cl + (C_6H_5)_3P \rightarrow$$
$$C_6H_5CH{=}CHCH_2P^+(C_6H_5)_3; Cl^-$$
$$C_6H_5CH{=}CHCH_2P^+(C_6H_5)_3; Cl^- + C_6H_5CHO + LiOC_2H_5 \rightarrow$$
$$C_6H_5CH{=}CHCH{=}CHC_6H_5 + (C_6H_5)_3PO + C_2H_5OH + LiCl$$
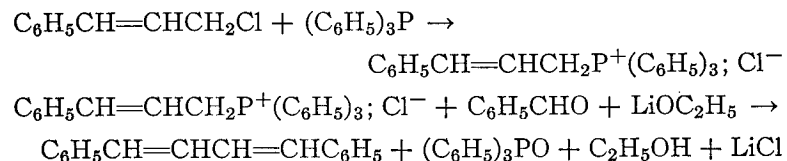
Submitted by Richard N. McDonald and Tod W. Campbell.[1]
Checked by M. S. Newman, R. Marshall, and W. N. White.

1. Procedure

A. *Triphenylcinnamylphosphonium chloride.* A mixture of 40 g. (0.26 mole) of (3-chloropropenyl)benzene (Note 1) and 92 g. (0.35 mole) of triphenylphosphine (Note 2) in 500 ml. of xylene is heated at reflux for 12 hours with stirring. The mixture is allowed to cool to about 60°, and the colorless crystalline product is filtered, washed with 100 ml. of xylene, and dried in a vacuum oven at about 20 mm. pressure and 60° to constant weight. The yield is 99–101 g. (91–93%), m.p. 224–226° (Note 3).

B. *1,4-Diphenylbutadiene.* To a solution of 60.0 g. (0.145 mole) of triphenylcinnamylphosphonium chloride and 16.4 g.

(0.155 mole) of benzaldehyde in 200 ml. of ethanol (Note 4) is added 760 ml. of 0.2M lithium ethoxide in ethanol (Notes 5 and 6). After allowing this mixture to stand 30 minutes, 700 ml. of water is added (Note 7) and the colorless crystals are filtered, washed with 150 ml. of 60% ethanol, and dried in the vacuum oven at 65°. The yield of crystalline product, m.p. 153–156°, is 17.9–19.9 g. (60–67%) (Note 8). The product is the *trans-trans* isomer and is pure enough for most purposes (Note 9). Recrystallization from cyclohexane gives a product with m.p. 154–156°.

2. Notes

1. Eastman Organic Chemicals, white label grade, used without purification.

2. Commercial triphenylphosphine was used without further purification. Metal and Thermit Corp., Rahway, New Jersey, now offers this reagent for sale at a modest price.

3. The phosphonium salt can be recrystallized to analytical purity by dissolving in a small amount of boiling ethanol, adding ether at the boil until cloudy, and allowing the salt to crystallize in a refrigerator.

4. Commercial anhydrous ethanol was used throughout without further purification.

5. The lithium ethoxide solution is prepared by dissolving 1.40 g. of lithium wire in 1 l. of anhydrous ethanol.

6. A transient orange color is immediately formed, and it is replaced by crystallization of the product in about 1 minute.

7. Triphenylphosphine oxide is soluble in 60% aqueous ethanol; therefore it remains in the filtrate and affords no difficulty.

8. The yield can probably be increased by carrying out the reaction in an ether solvent with an alkyllithium as base, but the simplicity and relative ease of the conditions described appear to make the possible yield advantage secondary.

9. This procedure has been applied successfully to the synthesis of substituted bistyryls, i.e., 1-(p-tolyl)-4-phenylbutadiene (76%), 1-(4-methoxyphenyl)-4-phenylbutadiene (63%), and 1-(4-acetamidophenyl)-4-phenylbutadiene (61%), by using the corresponding substituted benzaldehydes.

3. Methods of Preparation

1,4-Diphenylbutadiene has been obtained from phenylacetic acid and cinnamaldehyde with lead oxide,[2] by the dehydrogenation of 1,4-diphenyl-2-butene with butyllithium,[3] and by the coupling reaction of benzenediazonium chloride and cinnamylideneacetic acid.[4] The present method [5] gives better yields than those previously reported, is adaptable to the preparation of a variety of substituted bistyryls, and is relatively easy to carry out.

[1] Pioneering Research Division, Textile Fibers Department, E. I. du Pont de Nemours and Co., Wilmington, Delaware.

[2] B. B. Corson, *Org. Syn.*, Coll. Vol. 2, 229 (1943). This reference includes previous preparative methods.

[3] H. Gilman and C. W. Bradley, *J. Am. Chem. Soc.*, **60**, 2333 (1938).

[4] C. F. Koelsch and V. Boekelheide, *J. Am. Chem. Soc.*, **66**, 412 (1944).

[5] T. W. Campbell and R. N. McDonald, *J. Org. Chem.*, **24**, 1241. (1959).

α,β-DIPHENYLPROPIONIC ACID

(Propionic acid, 2,3-diphenyl-)

$$C_6H_5-CH_2-CO_2H \xrightarrow[\text{Liq. NH}_3]{\text{2NaNH}_2} C_6H_5-\underset{\underset{Na}{|}}{C}HCO_2Na \xrightarrow[\text{Et}_2O]{C_6H_5CH_2Cl}$$

$$C_6H_5-\underset{\underset{C_6H_5-CH_2}{|}}{C}H-CO_2Na \xrightarrow{H^+} C_6H_5-\underset{\underset{C_6H_5-CH_2}{|}}{C}H-COOH$$
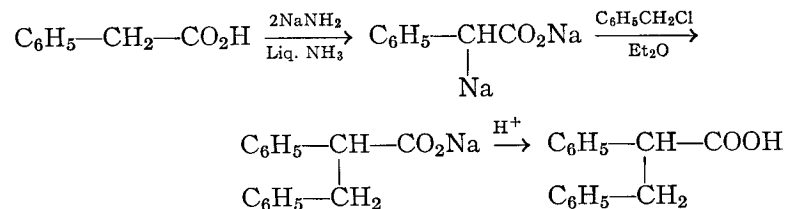
Submitted by CHARLES R. HAUSER and W. R. DUNNAVANT.[1]
Checked by VIRGIL BOEKELHEIDE and P. WARRICK.

1. Procedure

Caution! This preparation should be carried out in a hood to avoid exposure to ammonia.

A solution of sodium amide (0.226 mole) in liquid ammonia is prepared in a 1-l. three-necked flask equipped with a condenser, a ball-sealed mechanical stirrer, and a dropping funnel. Commercial anhydrous liquid ammonia (500 ml.) is introduced from

a cylinder through an inlet tube. To the stirred ammonia is added a small piece of sodium. After the appearance of a blue color, a few crystals of ferric nitrate hydrate (about 0.25 g.) are added, followed by small pieces of freshly cut sodium until 5.2 g. has been added. After all the sodium has been converted to the amide (Note 1), 14.2 g. (0.104 mole) of phenylacetic acid (Note 2) is added and the dark-green suspension is stirred for 15 minutes. To the green suspension is added rapidly 13.2 g. (0.104 mole) of benzyl chloride (Note 3) in 25 ml. of anhydrous ether, and the mixture is then stirred for 1 hour. The mixture is then evaporated to near dryness on a steam bath, 200 ml. of ether added, and evaporation to dryness effected. Another 200 ml. of ether is added, followed by evaporation to dryness. The resulting solid is then dissolved in 300 ml. of water and washed with three 200-ml. portions of ether. The aqueous solution is filtered through a layer of Celite to remove the slight brown coloration, and the filtrate is acidified with hydrochloric acid. A colorless oil forms which, when cooled for a few minutes in an ice bath, becomes a white crystalline solid. This is collected by filtration and washed with three 100-ml. portions of hot water (Note 4) and dried. The yield of crude α,β-diphenylpropionic acid, m.p. 92.0–93.5°, is 19.85 g. (84.5–88%). The crude solid is recrystallized from 60 ml. of petroleum ether (60–90°) to yield 18.80 g. (80–84%) (Note 5) of α,β-diphenylpropionic acid, m.p. 95.5–96.5° (Notes 6 and 7).

2. Notes

1. Conversion is indicated by the disappearance of any blue color. This generally requires about 20 minutes.

2. Phenylacetic acid as supplied by the Eastman Kodak Company was used without purification.

3. Eastman Kodak Company "Practical Grade" benzyl chloride was distilled before use, the fraction with b.p. 63–64°/12 mm. being used.

4. The hot water effectively removes unreacted phenylacetic acid, m.p. 76.7°, the presence of which hinders the purification of the product. The water should be hot but not boiling, since

α,β-diphenylpropionic acid has some solubility in boiling water and may be recrystallized from water.

5. An identical preparation using potassium amide instead of sodium amide gave α,β-diphenylpropionic acid in 57% yield.

6. Miller and Rohde [7] report that α,β-diphenylpropionic acid exists in three crystalline modifications melting at 82°, 88–89°, and 95–96°. Although the product obtained by the submitters melted at 95.5–96.5°, corresponding to the high-melting form, the sample obtained by the checkers melted sharply at 88–89° corresponding to the crystalline form of intermediate melting point.

7. Under comparable conditions the corresponding alkylations of phenylacetic acid with α-phenylethyl chloride and benzhydryl chloride have been effected to form α,β-diphenylbutyric acid and α,β,β-triphenylpropionic acid in yields of 74% and 51%, respectively.[2]

3. Methods of Preparation

This procedure is an adaption of one described by Hauser and Chambers.[2] Previous preparations include the benzylation of diethyl phenylmalonate followed by hydrolysis,[3] the benzylation of phenylacetonitrile followed by hydrolysis,[4,5] the benzylation of phenylacetic acid through the Ivanov reagent,[6] and the reduction of α-phenylcinnamic acid using sodium amalgam.[7]

The present procedure illustrates the use of dianions for alkylation and gives α,β-diphenylpropionic acid more conveniently and in better yield than previous preparations.

[1] Department of Chemistry, Duke University, Durham, North Carolina. Work supported by the Office of Ordnance Research.

[2] C. R. Hauser and W. J. Chambers, *J. Am. Chem. Soc.*, **78**, 4942 (1956).

[3] W. Wislicenus and K. Goldstein, *Ber.*, **28**, 818 (1895).

[4] A. Meyer, *Ber.*, **21**, 1311 (1888).

[5] C. R. Hauser and W. R. Brasen, *J. Am. Chem. Soc.*, **78**, 494 (1956).

[6] T. Cohen and G. F. Wright, *J. Org. Chem.*, **18**, 432 (1953).

[7] W. v. Miller and G. Rohde, *Ber.*, **25**, 2017 (1892).

3-ETHOXY-2-CYCLOHEXENONE

(Dihydroresorcinol monoethyl ether)

$$+ \; C_2H_5OH \; \xrightarrow{p\text{-}CH_3C_6H_4SO_3H} \; + \; H_2O$$
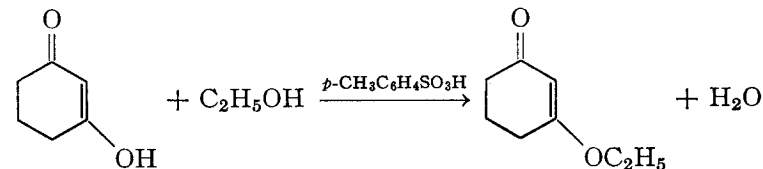
Submitted by WALTER F. GANNON and HERBERT O. HOUSE.[1]
Checked by WILLIAM E. PARHAM, WAYLAND E. NOLAND, GEORGE MEISTERS, and ALLAN M. HUFFMAN.

1. Procedure

In a 2-l. flask fitted with a total-reflux, variable-take-off distillation head is placed a solution of 53 g. (0.472 mole) of dihydroresorcinol (Note 1), 2.3 g. of p-toluenesulfonic acid monohydrate and 250 ml. of absolute ethanol in 900 ml. of benzene. The mixture is heated to boiling and the azeotrope composed of benzene, alcohol, and water is removed at the rate of 100 ml. per hour. When the temperature of the distilling vapor reaches 78° (Note 2), the distillation is stopped and the residual solution is washed with four 100-ml. portions of 10% aqueous sodium hydroxide which have been saturated with sodium chloride. The resulting organic solution is washed with successive 50-ml. portions of water until the aqueous washings are neutral and then concentrated under reduced pressure. The residual liquid is distilled under reduced pressure. The yield of 3-ethoxy-2-cyclohexenone (Note 3), b.p. 66–68.5°/0.4 mm. or 115–121°/11 mm., n_D^{29} 1.5015, is 46.6–49.9 g. (70–75%).

2. Notes

1. The preparation of dihydroresorcinol was described in an earlier volume of this series.[2]

2. This distillation requires 6–8 hours.

3. The product may be analyzed by gas chromatography on an 8 mm. x 215 cm. column heated to 220–240° and packed with Dow-Corning Silicone Fluid No. 550 suspended on 50–80 mesh ground firebrick. The chromatogram obtained with this column exhibits a single major peak. The ultraviolet spectrum of an ethanol solution of the product has a maxium at 250 mμ (ε = 17,200).

3. Methods of Preparation

3-Ethoxy-2-cyclohexenone has been prepared by reaction of the silver salt of dihydroresorcinol with ethyl iodide [3] and by the reaction of dihydroresorcinol with ethyl orthoformate, ethanol and sulfuric acid.[4] The acid-catalyzed reaction of dihydroresorcinol with ethanol in benzene solution utilized in this preparation is patterned after the procedure of Frank and Hall.[4,5]

4. Use of 3-Ethoxy-2-cyclohexenone

3-Ethoxy-2-cyclohexenone is a useful intermediate in the synthesis of certain cyclohexenones. The reduction of 3-ethoxy-2-cyclohexenone with lithium aluminum hydride followed by hydrolysis and dehydration of the reduction product yields 2-cyclohexenone.[6] Similarly, the reaction of 3-ethoxy-2-cyclohexenone with Grignard reagents followed by hydrolysis and dehydration of the addition product affords a variety of 3-substituted 2-cyclohexenones.[3,5]

[1] Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts.
[2] Org. Syntheses, Coll. Vol. 3, 278 (1955).
[3] G. F. Woods and I. W. Tucker, J. Am. Chem. Soc., 70, 2174 (1948).
[4] E. G. Meek, J. H. Turnbull, and W. Wilson, J. Chem. Soc., 1953, 811.
[5] R. L. Frank and H. K. Hall, Jr., J. Am. Chem. Soc., 72, 1645 (1950).
[6] See p. 14, this volume.

ETHYL 6,7-DIMETHOXY-3-METHYLINDENE-2-CARBOXYLATE

(Indene, 6,7-dimethoxy-3-methyl-2-carbethoxy-)
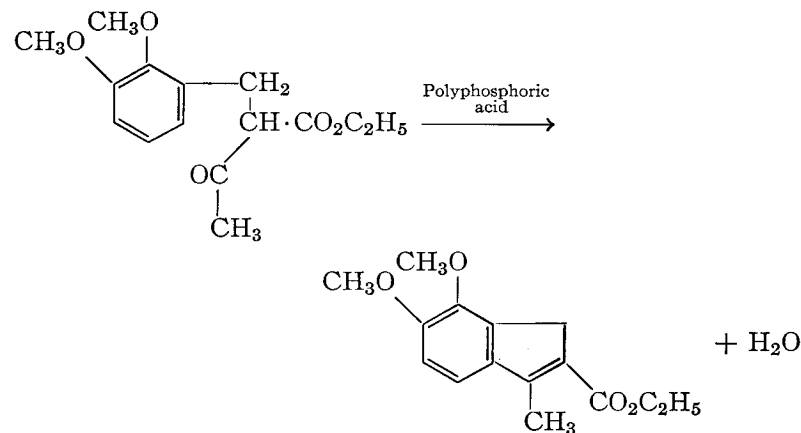
Submitted by John Koo.[1]
Checked by John C. Sheehan and J. Iannicelli.

1. Procedure

To 300 g. of polyphosphoric acid (Note 1) precooled to 5° is added 28 g. (0.1 mole) of ethyl α-acetyl-β-(2,3-dimethoxyphenyl)-propionate [2] contained in a 400-ml. beaker. The mixture is stirred thoroughly (Note 2) with a strong spatula for 15 minutes. The temperature, which is around 10° at the beginning, increases rapidly and is kept between 20° and 25° by occasionally cooling the beaker in an ice-water bath (Note 3). The deep-yellow reaction paste is then poured immediately into 600 ml. of ice water with thorough stirring and trituration (Note 4), and the beaker is rinsed with small portions of cold water. The product, which separates from the cold water as a colorless precipitate, is extracted with several portions of chloroform (first with 400 ml.,

then twice with 200 ml., and finally with 100 ml. of this solvent). The combined chloroform extracts are washed successively with 100 ml. of cold water, then once with 100 ml., twice with 50 ml. of 10% sodium bicarbonate solution (Note 5), and finally with 50 ml. of cold water. The chloroform solution is dried over magnesium sulfate and filtered. The chloroform is removed by distillation on a steam bath first at atmospheric pressure and finally under reduced pressure. The residual pale-yellow oil soon solidifies and is practically pure. The yield of ethyl 6,7-dimethoxy-3-methylindene-2-carboxylate is 21.5–22.5 g. (82–86%), m.p. 81–83° (Note 6).

2. Notes

1. Obtained from Victor Chemical Works, Chicago, Illinois.

2. Since the mixture is so viscous, continuous and vigorous hand stirring is necessary.

3. After the reaction starts, the temperature should be checked every few minutes and kept between 20° and 25°, which is the most favorable temperature.

4. Careful stirring and trituration are necessary to ensure the complete decomposition of every drop of the yellow paste.

5. According to the submitter, acidification of the combined sodium bicarbonate washings with 10% hydrochloric acid yields a colorless precipitate of 6,7-dimethoxy-3-methylindene-2-carboxylic acid, which is collected by filtration, washed, and dried; yield, 3.4–3.9 g. (14–16%); m.p. 216–218°.

6. Recrystallization from 75 ml. of 60% ethanol gives a 90% recovery of colorless long needles, m.p. 83–85°.

3. Methods of Preparation

The method described here is based on the analogous preparation of some other indenes.[3]

[1] Present address: National Drug Company, Research Laboratories, Philadelphia 44, Pennsylvania. Work done in the Laboratory of Chemical Pharmacology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.
[2] *Org. Syntheses*, **31**, 56 (1951).
[3] J. Koo, *J. Am. Chem. Soc.*, **75**, 1891 (1953).

FERROCENYLACETONITRILE

{Iron, [(cyanomethyl)cyclopentadienyl]cyclopentadienyl-}
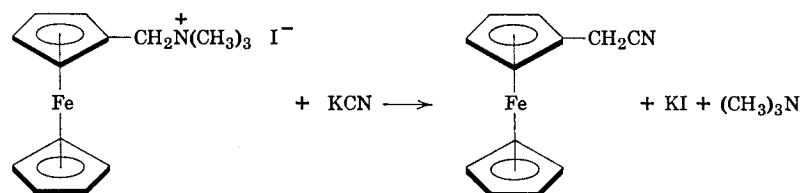
Submitted by Daniel Lednicer and Charles R. Hauser.[1]
Checked by B. C. McKusick and R. D. Vest.

1. Procedure

Caution! This preparation should be carried out in a hood since trimethylamine is evolved.

A solution of 57 g. (0.88 mole) of potassium cyanide in 570 ml. of water is placed in a 1-l. three-necked flask equipped with a stirrer and a reflux condenser. Fifty-eight grams (0.15 mole) of N,N-dimethylaminomethylferrocene methiodide[2] is added and the mixture is heated to boiling with good stirring. As the mixture is brought to boiling, the solid goes into solution. Within a few minutes of the onset of boiling, evolution of trimethylamine begins and a steam-volatile oil starts to separate from the solution. The reaction mixture is boiled vigorously with stirring for 2 hours and then is allowed to cool to room temperature. During the cooling the oil that has separated solidifies.

The solid is separated by filtration and the filtrate is extracted with three 150-ml. portions of ether. (*Caution! Gloves should be worn when handling this solution because of the large amount of cyanide it contains.*) The solid is dissolved in ether and this solution is combined with the extracts. The combined ethereal solutions are washed with water and dried over 5 g. of sodium sulfate. Removal of the solvent by distillation leaves crude ferrocenylacetonitrile as a solid or as an oil that crystallizes on being scratched. The nitrile is dissolved in about 200 ml. of boiling

technical grade hexane. The hot solution is decanted from a small amount of insoluble black tar and is cooled to room temperature. Ferrocenylacetonitrile is deposited as bright yellow crystals, m.p. 79–82° (Note 1). The yield of the nitrile is 24–26 g. (71–77%) (Note 2).

2. Notes

1. The pure nitrile melts at 81–83° after further recrystallization from hexane.[3]

2. The yield is directly dependent on the quality of the methiodide employed. Yields as high as 95% have been obtained.[3]

3. Methods of Preparation

This method is that described by Lednicer, Lindsay, and Hauser.[3] No other procedure appears to have been employed to prepare this compound.

Essentially the present procedure converted 1-methylgramine to 1-methyl-3-indoleacetonitrile,[4] but it failed to convert benzyl-dimethylphenylammonium chloride to phenylacetonitrile.[5]

[1] Department of Chemistry, Duke University, Durham, North Carolina. The work was supported by the Office of Ordnance Research, U. S. Army.

[2] See p. 31, this volume.

[3] D. Lednicer, J. K. Lindsay, and C. R. Hauser, *J. Org. Chem.*, **23**, 653 (1958).

[4] H. R. Snyder and E. L. Eliel, *J. Am. Chem. Soc.*, **70**, 1857 (1948).

[5] H. R. Snyder and J. C. Speck, *J. Am. Chem. Soc.*, **61**, 668 (1939).

3-(2-FURYL)ACRYLONITRILE

(2-Furanacrylonitrile)
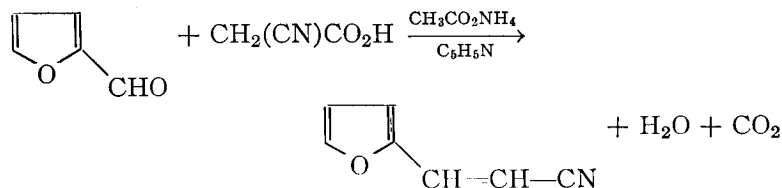
Submitted by John M. Patterson.[1]
Checked by Melvin S. Newman and Herbert Boden.

1. Procedure

A mixture of 105.6 g. (1.1 moles) of freshly distilled furfural, 87.0 g. (1.0 mole) of 98% cyanoacetic acid (Note 1), 3.0 g. of ammonium acetate, 200 ml. of toluene, and 110 ml. of pyridine is placed in a 1-l. round-bottomed flask equipped with a Stark and Dean water trap and reflux condenser. The mixture is boiled under reflux for 2 days. The theoretical quantity of water is collected in the trap within 1 hour. Upon completion of the reflux period, the solvent is removed under reduced pressure by heating on a water bath. The residue, distilled through a 15-cm. Vigreux column at 11 mm. pressure, yields 88.6–93.3 g. (74.5–78%) of colorless liquid boiling at 95–97°, n_D^{25} 1.5823–1.5825.

2. Note

1. Cyanoacetic acid was obtained from Distillation Products Industries, Rochester, New York, and used without further purification.

3. Methods of Preparation

The method described is a modification of the procedure used by Ghosez[2] to synthesize cinnamonitrile. 3-(2-Furyl)acrylonitrile has been prepared by catalytic condensation of furfural with acetonitrile in the vapor phase at 320°,[3] by dehydration of the corresponding amide over phosphorus pentachloride,[4] and by decarboxylation of 3-(2-furyl)-2-cyanoacrylic acid.[5]

[1] University of Kentucky, Lexington, Kentucky.

[2] J. Ghosez, *Bull. soc. chim. Belges.*, **41**, 477 (1932).

[3] M. M. Brubaker, U. S. pat. 2,341,016 (1944) [*C.A.*, **38**, 4272 (1944)].

[4] H. Gilman and A. P. Hewlett, *Iowa State Coll. J. Sci.*, **4** (1), 27 (1929).

[5] R. Heuck, *Ber.*, **27**, 2624 (1894).

2-HYDROXYISOPHTHALIC ACID

(Isophthalic acid, 2-hydroxy-)
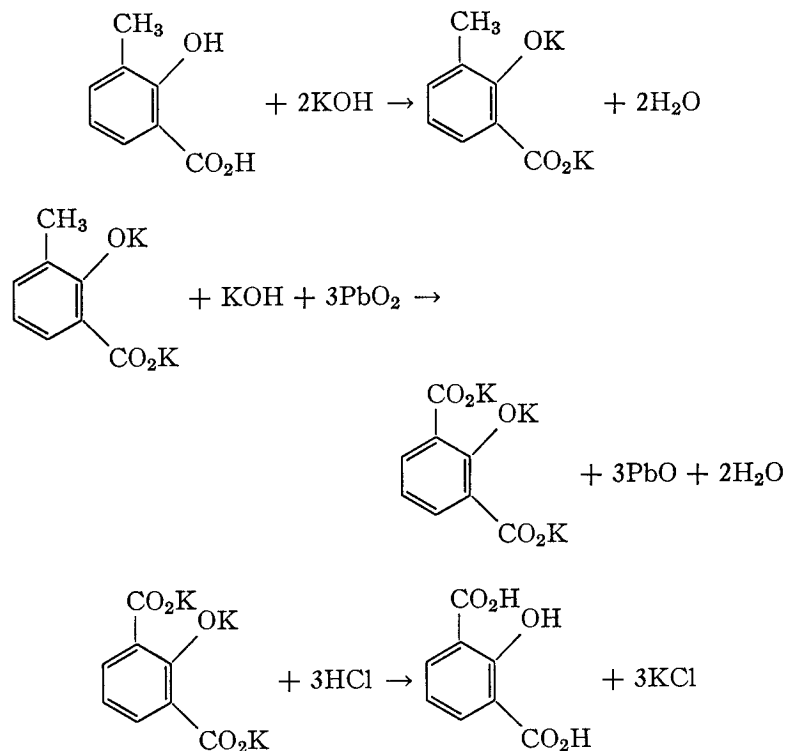
Submitted by DAVID TODD [1] and A. E. MARTELL.[2]
Checked by B. C. MCKUSICK and S. ANDREADES.

1. Procedure

In an 800-ml. stainless-steel flanged beaker are placed 240 g. of potassium hydroxide pellets and 50 ml. of water. When the mush has cooled, 40.0 g. (0.263 mole) of 2-hydroxy-3-methyl-benzoic acid (Note 1) is added, and the slurry is stirred with a long glass rod. The beaker is placed firmly in a clamp (Note 2) and set in a cold oil bath (Note 3) in a hood, and 240 g. (1.00 mole) of lead dioxide is stirred in all at once (Note 4). The oil

bath is now heated by a flame, and when the bath temperature reaches 200° steady manual stirring by means of the glass rod is begun. (*Caution! Goggles and a rubber glove should be worn to protect eyes and the stirring hand against spattering.*) The temperature is raised, with steady stirring, until the bath reaches 238–240°, when the flame is moderated to maintain this bath temperature. Several minutes after 240° is reached, the mixture boils steadily and the lumpy brown mass turns quickly to a bright-orange melt containing heavy crystals of lead monoxide. The bath is held at 240° for another 15 minutes. It is then brought briefly to 250°, the flame is removed, and the beaker is lifted out of the bath.

About 5 minutes later, the liquid contents of the beaker are poured cautiously into a 2-l. glass beaker, and this is tipped and rotated slowly so as to spread the congealing mass in a thin film on the beaker walls. When the material in the beakers has cooled, a total of 1 l. of water is poured into the beakers and the water is stirred well for at least 1 hour (Note 5). The cold suspension is filtered with suction to separate 200–210 g. of an insoluble mixture of lead monoxide and red lead, which is washed on the filter with six 50-ml. portions of water.

The alkaline filtrate and washings are combined and partially neutralized by the addition of 150–175 ml. of concentrated hydrochloric acid. Sufficient sodium sulfide solution is added to precipitate all the lead ion present (Note 6). The suspension is brought to a gentle boil to coagulate the lead sulfide, allowed to cool somewhat, and filtered with suction. The filtrate is placed in a 2-l. beaker set in an ice bath and acidified (*Caution! in the hood*) with about 150 ml. of concentrated hydrochloric acid to precipitate crude 2-hydroxyisophthalic acid monohydrate (Note 7). The suspension is cooled to 0–5° and filtered to separate the crude acid, which weighs 35–49 g. after being dried in a vacuum oven at 110°/50–150 mm. for 5 hours (Note 8).

In order to remove 1–3 g. of contaminating 2-hydroxy-3-methylbenzoic acid, the crude acid is ground in a mortar and refluxed briefly with 100 ml. of chloroform, and the suspension is filtered hot (Note 9). The separated solid is dried in air and added to 1 l. of boiling water. The mixture is boiled gently for 15 min-

utes and filtered by gravity to remove a small amount of gray sludge. The clear light-orange filtrate rapidly deposits needles of 2-hydroxyisophthalic acid monohydrate. After cooling to 0–5°, the acid is collected and dried at 110°/50–150 mm. for 20 hours. The anhydrous acid, which ranges in color from pale pink to tan, weighs 22–29 g. (46–61%) (Note 10) and melts at 243–255°, depending on the rate of heating and the apparatus used.

2. Notes

1. Eastman Kodak technical grade material is satisfactory.

2. A convenient clamp can be fashioned by bending a loop at the end of a 40-cm. length of iron rod 6 mm. (¼ in.) in diameter so that the beaker can just slip up to its flange through the loop. A pinch clamp is used to hold the flange firmly to the loop.

3. The checkers used a bath wax (flash point 325°) supplied by the Fisher Scientific Co. The operation should be carried out in a hood because fumes from oil baths at high temperatures are injurious to health. A fire extinguisher should be close at hand in case the oil bath catches fire. A high-boiling silicone heat exchange oil, although more expensive, would be less of a fire hazard. Alternatively, a sodium nitrite-sodium nitrate-potassium nitrate mixture such as "Hitec" heat transfer salt sold by the du Pont Company (useful range 150–450°) can be used. Such baths will not burn, but they have the disadvantage of being oxidizing agents, so precautions should be taken not to let any organic material get into them lest a flash oxidation accompanied by spattering of hot salt take place. Hot salt baths should be well shielded to guard against spattering.

4. If the calculated amount (190 g.) of lead dioxide is used, the yield is lowered by about 20%.

5. At least an hour's contact with water is necessary in order to dislodge all the solid from the walls.

6. The amount of sodium sulfide nonahydrate needed varies from 12 to 25 g. from one run to another.

7. The acid is precipitated from aqueous solution as the monohydrate, which is soluble in cold dilute hydrochloric acid to the extent of about 6 g. per l.

8. An additional 3–5 g. (6–10%) of crude product can be obtained by concentrating the filtrate to about 800 ml., cooling the concentrate to 0°, and filtering the solid that separates. This solid must be washed well with cold water to remove coprecipitated potassium chloride.

9. The starting material is moderately soluble in hot chloroform, while 2-hydroxyisophthalic acid is quite insoluble. Fractional crystallization from water, an alternative method suggested for the separation of starting material,[3] has been found by the submitters to be unsuccessful.

10. An additional 2–5 g. (4–10%) of product can be obtained by concentrating the filtrate to one-third its volume, adding 25 ml. of concentrated hydrochloric acid, cooling the mixture, separating crude acid by filtration, and recrystallizing the acid from water.

3. Methods of Preparation

2-Hydroxyisophthalic acid has been prepared by oxidizing 2-hydroxy-3-methylbenzoic acid with lead dioxide,[3,4] by cleaving the ether group of 2-methoxyisophthalic acid with hydriodic acid,[5] and by hydrolyzing 2-iodoisophthalic acid with alcoholic sodium hydroxide.[6]

The lead dioxide-alkali method has also been applied successfully by Graebe and Kraft [4] to the three cresols, the three toluic acids, and 2,4-dimethylphenol. For the preparation of 2-hydroxyisophthalic acid, it is the only one-step method that starts from readily obtainable materials.

In general, this method is a one-step procedure for the oxidation of a cresol type of molecule to the corresponding phenolic acid. The vigorous reaction conditions clearly limit the type of functional groups that may be present in the molecule. There is no evidence that the reaction has been applied to polynuclear or heterocyclic alkylphenols.

[1] Worcester Polytechnic Institute, Worcester, Massachusetts.
[2] Clark University, Worcester, Massachusetts.
[3] W. S. Benica and O. Gisvold, *J. Am. Pharm. Assoc., Sci. Ed.*, **34**, 42 (1945).
[4] C. Graebe and H. Kraft, *Ber.*, **39**, 799 (1906).
[5] G. R. Sprengling and J. H. Freeman, *J. Am. Chem. Soc.*, **72**, 1984 (1950).
[6] C. W. James, J. Kenner, and W. V. Stubbings, *J. Chem. Soc.*, **117**, 775 (1920).

HYDROXYMETHYLFERROCENE

{Iron, cyclopentadienyl[(hydroxymethyl)cyclopentadienyl]-}

$$\text{Fe} \quad + \text{ NaOH} \longrightarrow \quad \text{Fe} \quad + \text{ NaI} + (CH_3)_3N$$
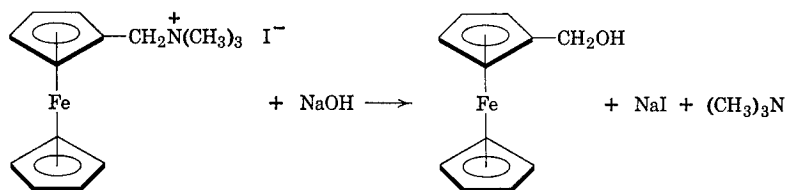
Submitted by Daniel Lednicer, T. Arthur Mashburn, Jr.,
and Charles R. Hauser.[1]
Checked by B. C. McKusick, H. F. Mower, and G. N. Sausen.

1. Procedure

Caution! This preparation should be conducted in a hood because trimethylamine is evolved.

A solution of 10.0 g. (0.25 mole) of sodium hydroxide in 250 ml. of water is prepared in a 1-l. round-bottomed flask equipped with a reflux condenser and a mechanical stirrer. Twenty-five grams (0.065 mole) of N,N-dimethylaminomethylferrocene methiodide [2] is added to the solution. The resulting suspension is heated to reflux temperature with stirring. At this point the solid is in solution. Within 5 minutes oil starts to separate from the solution and trimethylamine starts to come off. At the end of 3.5 hours, at which time the evolution of the amine has virtually ceased, the reaction mixture is allowed to cool to room temperature. The oil generally crystallizes during the cooling. The mixture is stirred with 150 ml. of ether until the oil or solid is all dissolved in the ether. The ether layer is separated in a separatory funnel and the aqueous layer is extracted with two additional 150-ml. portions of ether. The combined ether extracts are washed once with water and dried over sodium sulfate.

The oil that remains when the solvent is removed from the extract crystallizes when cooled to room temperature. This orange solid is recrystallized from 150 ml. of hexane (Note 1) to yield 9.5–12.5 g. (68–89%) of hydroxymethylferrocene, m.p. 74–76°. One more recrystallization from the same solvent affords 8.2–11.0 g. (59–79%) (Note 2) of good-quality alcohol as golden needles, m.p. 76–78° (Note 3).

2. Notes

1. Eastman Kodak Company practical grade hexane is suitable.
2. The yield of this reaction is directly dependent on the purity of the quaternary salt employed. If the salt is prepared from redistilled N,N-dimethylaminomethylferrocene, the yield of alcohol may be as high as 90%.[3]
3. The pure alcohol melts at 81–82°.

3. Methods of Preparation

Hydroxymethylferrocene has been made by condensing ferrocene with N-methylformanilide to give ferrocenecarboxaldehyde, and reducing the latter with lithium aluminum hydride,[4] sodium borohydride,[5] or formaldehyde and alkali.[5] The present procedure is based on the method of Lindsay and Hauser.[3] A similar procedure has been used to convert gramine methiodide to 3-hydroxymethylindole,[6] and the method could probably be used to prepare other hydroxymethyl aromatic compounds.

[1] Department of Chemistry, Duke University, Durham, North Carolina. The work was supported by the Office of Ordnance Research, U. S. Army.
[2] See p. 31, this volume.
[3] J. K. Lindsay and C. R. Hauser, *J. Org. Chem.*, **22**, 355 (1957).
[4] P. J. Graham, R. V. Lindsey, G. W. Parshall, M. L. Peterson, and G. M. Whitman, *J. Am. Chem. Soc.*, **79**, 3416 (1957).
[5] G. D. Broadhead, J. M. Osgerby, and P. L. Pauson, *J. Chem. Soc.*, **1958**, 650.
[6] E. Leete and L. Marion, *Can. J. Chem.*, **31**, 775 (1953).

3-HYDROXYQUINOLINE

(3-Quinolinol)

A. $CH_3COCO_2H + SO_2Cl_2 \rightarrow ClCH_2COCO_2H + SO_2 + HCl$

B.

C.
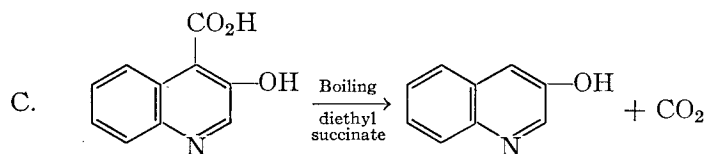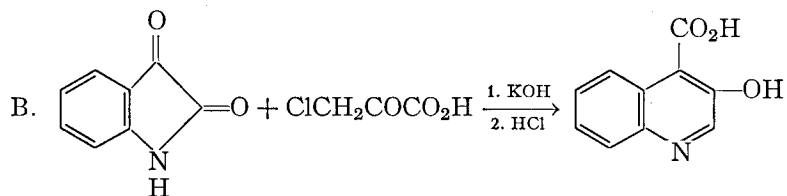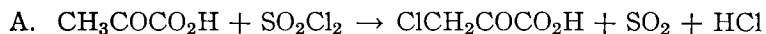
Submitted by Edward J. Cragoe, Jr., and Charles M. Robb.[1]
Checked by James Cason and James D. Willett.

1. Procedure

Caution! The preparation of chloropyruvic acid should be carried out in a fume hood, as should the purification of 3-hydroxycinchoninic acid and its decarboxylation.

A. *Chloropyruvic acid.* In a 1-l. four-necked flask (Note 1) fitted with a sealed mechanical stirrer, dropping funnel, thermometer, and reflux condenser protected with a calcium chloride tube is placed 249 g. (2.83 moles) of pyruvic acid (Note 2). The stirrer is started and 394 g. (2.92 moles) of sulfuryl chloride (Note 3) is added dropwise over a period of 2 hours. During the addition the temperature is maintained at 25–30° by cooling with a water bath.

The mixture is stirred at room temperature for an additional 60 hours (Note 4), during which time the calcium chloride tube may become spent and need replacement. The viscous, light-yellow liquid product is transferred to a large crystallizing dish and dried in a vacuum desiccator over soda-lime for about 24 hours (Note 5).

The yield of light-yellow chloropyruvic acid is 333–340 g. (96–98%) (Note 6).

B. *3-Hydroxycinchoninic acid.* A 3-l., four-necked flask (Note 1) is equipped with a sealed mechanical stirrer, gas inlet tube, gas outlet consisting of a 1-mm. capillary (Note 7), and thermometer. The flask is charged with a freshly prepared solution containing 448 g. (8 moles) of reagent grade (85% minimum assay) potassium hydroxide and 900 ml. of water. The solution (hot from dissolution of potassium hydroxide) is stirred and 147 g. (1 mole) of isatin (Note 8) is introduced. The solid quickly dissolves to give an orange-yellow solution.

After replacement of the gas outlet the flask is flushed with nitrogen, and a nitrogen atmosphere is maintained during the remaining operations (Note 9). The temperature is maintained at 20–25° by cooling when necessary. The solution is stirred vigorously as 168.5 g. (1.375 moles) of chloropyruvic acid (part A) is added gradually over a period of 2 hours (Note 10). After stirring has been continued for an additional hour, the introduction of nitrogen and the stirring are terminated, the flask is stoppered, and the mixture is allowed to stand at room temperature for 6 days.

At the end of the standing period the reaction mixture is cooled with stirring and maintained at 15–18°. A solution containing 34 g. of sodium bisulfite in 60 ml. of water (Note 11) is added, and the mixture is made acid to Congo red paper by the dropwise addition of reagent grade concentrated hydrochloric acid (Note 12) (approximately 480 ml.). The yellow product that precipitates is separated by suction filtration on a large (at least 15-cm.) Büchner (or sintered-glass) funnel and washed with water saturated with sulfur dioxide. Drainage of the filter cake, whose consistency is that of putty, is slow. Pressing with a large cork or use of a rubber dam is helpful. The pressed solid is suspended in 1.3 l. of water previously saturated with sulfur dioxide, and the mixture is mechanically stirred for 30 minutes.

After the product has been collected as before, the filter cake is pressed well, suspended in 800 ml. of water, and dissolved by stirring and adding the minimum quantity of reagent grade concentrated aqueous ammonia (approximately 60 ml.). A small

amount of insoluble material is removed by filtration. A saturated solution of 8 g. of sodium bisulfite is added to the filtrate. The orange-yellow solution is stirred mechanically and made acid to Congo red paper by the dropwise addition of reagent grade concentrated hydrochloric acid (approximately 80 ml.).

The product is again collected by filtration, washed with water, resuspended in 225 ml. of water, collected, and pressed as dry as possible. The filter cake is thoroughly dispersed in 160 ml. of absolute alcohol, then filtered, air-dried, and finally dried in a vacuum desiccator over concentrated sulfuric acid. The bright-yellow solid is pulverized and redried. The yield is 115–135 g. (60–71%). When this product is inserted in a bath preheated to 210° and the temperature is increased at a rate of 1° per 10 seconds, decomposition with evolution of gas occurs at 219–220° (cor.) (Note 13).

C. *3-Hydroxyquinoline.* A 1-l. beaker is fitted with a thermometer and mechanical stirrer and clamped firmly on an efficient electric heater (Note 14). Diethyl succinate (400 ml.) (Note 15) is placed in the beaker and heated to boiling (215–220°) with stirring. 3-Hydroxycinchoninic acid (part B) (94.6 g., 0.5 mole) is added in portions to the boiling solution by means of a metal spoon or Scoopula. Care is taken to prevent too vigorous evolution of carbon dioxide. The addition requires 2–3 minutes, during which time a temperature drop is noted unless good heating is maintained.

Stirring and boiling are continued until complete solution is effected. This requires about 6 minutes (Note 16). The stirrer is withdrawn and the beaker is removed from the hot plate for a few minutes. Finally, the solution is stirred and cooled first in a warm water bath and then in an ice bath. After 30 minutes the gray-brown solid is collected by suction filtration and washed with hexane. The product is suspended in 250 ml. of hexane, filtered, and washed with hexane. After drying, the crude gray-colored 3-hydroxyquinoline weighs 57–63 g. (79–87%), m.p. 175–191° (cor.).

The crude product is suspended in 190 ml. of water and dissolved by the addition of the minimum quantity (31–35 ml.) of concentrated hydrochloric acid. The solution is filtered in order to remove a small amount of insoluble material. The filtrate is treated with decolorizing carbon (about 3.5 g.), allowed to stand for 30 minutes, and filtered. The filtrate from the charcoal is stirred and treated dropwise with concentrated aqueous ammonia (25–29 ml.) until precipitation is complete. The precipitate is removed by filtration, washed with water (two 30-ml. portions), and dried. The yield at this stage is 48–55 g. of material melting at 185–195° (cor.).

The reprecipitated product is pulverized, dissolved in a boiling mixture of methanol (about 420 ml.) and water (about 360 ml.), and treated with decolorizing charcoal for about 10 minutes. The boiling mixture is filtered through a fluted filter paper placed on a large Pyrex funnel resting on a wide-mouthed Erlenmeyer flask containing a little boiling solvent of the same composition. The filtrate is concentrated to incipient precipitation (about 600 ml. volume) and allowed to cool. After drying, the yield of tan-colored crystalline 3-hydroxyquinoline is 44–47 g. (61–65%), m.p. 199–200° (cor.) (Note 17).

2. Notes

1. If suitable dual outlets are used, a three-necked flask is satisfactory.

2. Pyruvic acid from Matheson, Coleman and Bell was distilled just before use. Material boiling at 46–47° at 4 mm. was employed.

3. Technical grade sulfuryl chloride from Matheson, Coleman and Bell was found satisfactory.

4. The stirring prevents foaming and promotes the evolution of the gases.

5. It is advisable to change the desiccant at least once during the drying period.

6. The chloropyruvic acid prepared in this manner is satisfactory for use in the next reaction without purification. It often crystallizes to form a waxy solid or semisolid which is quite hygroscopic. The pure anhydrous material is reported [2] to melt at 45°, while the monohydrate obtained by other methods [3-5] melts at 57–58°. The chloropyruvic acid is normally used immediately,

but it has been stored successfully in a desiccator at room temperature for a few days or for longer periods in an airtight container in the refrigerator. Material which has been stored for long periods gives poorer yields in the Pfitzinger reaction (part B) than that which has been freshly prepared.

7. When solids are added to the flask, the gas outlet is replaced by a powder funnel and nitrogen flow is increased slightly. If a separatory funnel is used (cf. Note 10), a dual outlet is needed.

8. Commercial isatin from Eastman Kodak or Matheson, Coleman and Bell has been used, but poorer yields are obtained (about 10% less) than when purified material is employed. Purification by reprecipitation [6] or by recrystallization from glacial acetic acid [6] is equally satisfactory.

9. Maintaining an atmosphere of nitrogen minimizes the darkening of the reaction mixture due to air oxidation.

10. If the chloropyruvic acid remains essentially as a viscous liquid, it may be introduced via a dropping funnel containing a large-bore stopcock. If the material has set up to a waxy solid, it must be introduced in portions through a powder funnel.

11. If no precautions are observed, the reaction mixture rapidly darkens after acidification when exposed to air. The sulfur dioxide generated upon acidification of the sodium bisulfite largely prevents this discoloration; however, the precipitated product should be collected *without delay* of more than a few hours. The sulfur dioxide used in the wash water also protects the product.

12. At about the midpoint in the addition of acid, frothing tends to raise the precipitate out of the flask. Addition of a 1-ml. portion of ether controls the frothing. A second portion of ether may be required later, but the frothing subsides as the addition proceeds.

13. 3-Hydroxycinchoninic acid of this purity is adequate for decarboxylation. A sample recrystallized from dimethylformamide or 5N hydrochloric acid decomposes at 224° when observed as described before.

14. It is advantageous to use a mechanical stirrer, but successful reactions have been carried out using manual stirring. A run in which no stirring was employed gave acceptable results.

15. Commercial diethyl succinate from Carbide and Carbon

Chemicals Co. or from Eastman Organic Chemicals was found satisfactory. Nitrobenzene has been used successfully a number of times; however, it is considered a less desirable solvent to handle.

16. The heating time is kept to a minimum in order to reduce the darkening of the solution, which increases as the heating time is extended.

17. Once recrystallized, 3-hydroxyquinoline is pure enough for most purposes. One or two more recrystallizations are required to produce white crystals, m.p. 201–202° (cor.).

3. Methods of Preparation

The method of synthesis described for chloropyruvic acid is essentially that reported.[2] This procedure affords the product in excellent yields from readily available materials by a short, convenient route. Other less acceptable methods involve chlorination of pyruvic acid with sulfur dichloride [7] or hypochlorous acid [8] and the treatment of ethyl chloro(1-hydroxyheptyl)- or (α-hydroxybenzyl)oxalacetate γ-lactone with 50% hydrochloric acid.[3-5]

The procedure described for the preparation of 3-hydroxycinchoninic acid is adapted from that reported.[9] This synthesis is successful when bromopyruvic acid or its ethyl ester is substituted for chloropyruvic acid.[9] The reaction of isatin with chloropyruvic acid to produce 3-hydroxycinchoninic acid has been reported;[10] however, no details or physical properties were given. This method offers a decided advantage over the method involving diazotization of the difficultly accessible 3-aminocinchoninic acid.[11]

Until recent years the only syntheses of 3-hydroxyquinoline involved multistep processes, the last step of which consisted of the conversion of 3-aminoquinoline to 3-hydroxyquinoline via the diazonium salt.[12-14] Small quantities of quinoline have been oxidized to 3-hydroxyquinoline in low yields by using oxygen in the presence of ascorbic acid, ethylenediaminetetraacetic acid, ferrous sulfate, and phosphate buffer.[15] The decarboxylation of 3-hydroxycinchoninic acid in boiling nitrobenzene has been re-

ported.[9,11] The procedure described involves a simplified modification of this method.

[1] Merck Sharp and Dohme Research Laboratories, West Point, Pennsylvania.

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HYDROXYUREA

(Urea, hydroxy-)

$$NH_2CO_2C_2H_5 + NH_2OH \cdot HCl \xrightarrow{NaOH}$$
$$NH_2CONHOH + NaCl + C_2H_5OH$$
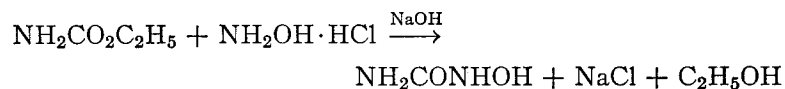
Submitted by R. Deghenghi.[1]
Checked by Melvin S. Newman and John Eberwein.

1. Procedure

To a solution of 20.8 g. (0.3 mole) of hydroxylamine hydrochloride and 20.6 g. (0.5 mole) of sodium hydroxide (98%) in 100 ml. of water is added 22.26 g. (0.25 mole) of ethyl carbamate. After 3 days at room temperature the solution is cooled in an ice bath and carefully neutralized with concentrated hydrochloric acid (Note 1). If necessary (Note 2), the solution is filtered and then extracted with ether; the aqueous phase is evaporated on a water bath under reduced pressure as rapidly as possible at a temperature not above 50–60°.

The dry residue is extracted by boiling with 100 ml. of absolute ethanol, and the solution is filtered through a heated funnel. On cooling, a first crop (6–8 g.) of hydroxyurea crystallizes.

The saline residue on the filter is extracted once again with 50 ml. of boiling absolute ethanol. On concentrating the filtrate from the second extraction and the mother liquor from the first crystallizate to a small volume, a second crop (4–6 g.) of product is obtained. The yield of the hydroxyurea is 10–14 g. (53–73%) of white crystals, m.p. 137–141° (dec.).

The product may be purified by recrystallization of 10 g. from 150 ml. of absolute ethanol. The rate of solution is slow (15–30 minutes is required), and the yield of hydroxyurea, m.p. 139–141° (dec.), is about 8 g. (Note 3).

2. Notes

1. Neutralization to phenolphthalein is satisfactory, but a glass electrode might give better results. Hydroxyurea is decomposed very rapidly in aqueous acidic medium, whereas its metallic salts (sodium or the copper complex salts) are stable.

2. Insoluble matter is sometimes present if a commercial grade of reactants is employed.

3. It is preferable to store the crystals in a cool, dry place. Some decomposition may occur after a few weeks.

3. Methods of Preparation

The improved method herein described is adapted from the procedure of Runti and Deghenghi.[2] Hydroxyurea has been prepared from potassium cyanate and hydroxylamine hydrochloride.[3-5] A lower melting isomeric substance, m.p. 71°, has been described.[4-6] The structure $NH_2CO_2NH_2$ has been proposed [5,6] for this low-melting substance.

[1] Department of Medical Research, University of Western Ontario, Ontario, Canada.

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METHANESULFINYL CHLORIDE

$$CH_3SSCH_3 + 3Cl_2 \rightarrow 2CH_3SCl_3$$

$$CH_3SCl_3 + CH_3CO_2H \rightarrow CH_3SOCl + CH_3COCl + HCl$$
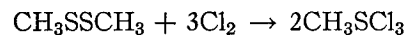
Submitted by Irwin B. Douglass and Basil Said Farah.[1]

Checked by Melvin S. Newman, J. T. Golden, and W. N. White.

1. Procedure

In a 1-l. three-necked flask, fitted with an efficient sealed stirrer, a gas inlet tube extending within 1 in. of the reaction mixture but not below its surface, and a gas outlet tube leading through a trap cooled in a dry ice-acetone bath to a hydrogen chloride absorption system (Note 1), are placed 94.2 g. (1 mole) of methyl disulfide (Note 2) and 120 g. (2 moles) of glacial acetic acid. The reaction flask is then surrounded by a bath of acetone cooled by dry ice until the internal temperature has reached 0° to −10°. The temperature is maintained within these limits throughout the reaction (Note 3) except that, toward the end, the temperature should be kept at −10° to −15° to minimize the escape of hydrogen chloride which might carry with it unreacted chlorine. The entire reaction is best carried out in a well-ventilated hood.

Three moles of chlorine (212.7 g.) is condensed in a tared flask cooled by a dry ice-acetone bath (Note 4). This flask is then connected to the gas inlet tube of the chlorination apparatus, and the cooling bath surrounding the chlorine container is removed. After about 2 hours the chlorine has all been absorbed by the reaction mixture (Note 5).

When the last of the chlorine has been added, the cooling bath is removed and, while vigorous stirring is continued (Note 6), the reaction mixture is allowed slowly to warm to room temperature. During this period there is a vigorous evolution of

hydrogen chloride. The flask is finally warmed to 35° to facilitate the escape of more hydrogen chloride.

The reaction mixture and contents of the cold trap are then transferred (Note 7) to a 500-ml. distilling flask attached through a short fractionating column to a water-cooled condenser which is connected in series to a receiver, a trap cooled in a dry ice-acetone bath, and a hydrogen chloride absorption trap which may later be attached to a water pump. The mixture is then distilled until the pot temperature reaches 100° and practically all of the acetyl chloride has been driven over.

The residue, consisting chiefly of methanesulfinyl chloride, is then cooled immediately to 20° or lower and transferred to a 250-ml. flask and distilled through the same equipment under reduced pressure to remove the remaining acetyl chloride and other lower-boiling impurities. As the pot temperature begins to rise, a yellow intermediate fraction is collected very slowly until the distillate and pot temperatures are within 3° of each other (Note 8). At this point the distillation is temporarily discontinued while the accumulated acetyl chloride (Note 9) is removed from the cold trap and the receiver for the main product is attached. On resuming distillation the main product should come over within a 5° boiling range, and the distillation and pot temperature should remain within 2° of each other until the major part of the product has distilled. The yield is 161–177 g. (82–92%) of straw-colored or yellow product boiling at 55–59° (40 mm.) and having n_D^{25} 1.500–1.501 (Note 10).

2. Notes

1. The hydrogen chloride absorption system must be of such design that there is no possibility for water to suck back into the reaction flask after a sudden surge of escaping hydrogen chloride.

2. The methyl disulfide was obtained from the Crown Zellerbach Corporation, Chemical Products Division, Camas, Washington, and redistilled. The 108–109° boiling fraction was used.

3. Crystalline acetic acid separates at first but redissolves as the reaction progresses.

4. The flask should be full of chlorine gas when the tare weight is taken. The success of this preparation depends in large measure on the use of stoichiometric quantities of all reagents. An excess or deficiency of any one will lead to an impure product and will greatly complicate the problem of purification.[2]

5. The white solid which collects inside the upper part of the flask is methylsulfur trichloride. This must be washed down with the cold reaction mixture before the flask warms to room temperature. The progress of the chlorination is accompanied by definite color changes. When one-third of the chlorine has been added, the reaction mixture is a deep reddish orange color which gradually fades as more chlorine is added until at the end the color should be a pale golden yellow or light straw color.

6. Vigorous stirring is necessary to prevent loss of material through too rapid escape of hydrogen chloride.

7. Since both methanesulfinyl and acetyl chlorides are unpleasant materials and the reaction mixture still contains much hydrogen chloride, all transfers should be made in the hood.

8. The difference between the distillation and pot temperatures is closely related to the success of this preparation. If the specified weights of reactants and temperatures are employed a 3° temperature difference should be reached before the yellow intermediate fraction, probably containing methanesulfenyl chloride, chloromethanesulfenyl chloride, and acetic acid, has attained a volume of 10 ml. Toward the end of the distillation the pot temperature may begin to rise owing to the presence in the residue of methanesulfonyl chloride (b.p. 63°/20 mm., 72°/31 mm., 82°/48 mm.), methyl methanethiolsulfonate (b.p. 115°/15 mm.) or both. The residue at the end of the distillation should amount to less than 10 ml.

9. The acetyl chloride obtained is yellow in color, probably because of the presence of the sulfenyl chlorides mentioned above. The addition of cyclohexene will discharge the color (although a darker color develops later) and redistillation then yields a stable water-clear product. The yield of acetyl chloride varies from 60% to 85%, depending on the care with which liquids are transferred and the vapors are trapped. The amount

of sulfinyl chloride which may be recovered by redistilling the acetyl chloride fraction does not justify the time required.

10. Pure methanesulfinyl chloride boils at 48° (22 mm.) and 59° (42 mm.) and has n_D^{25} 1.5038, d_4^0 1.4044 and d_4^{25} 1.3706. On standing at room temperature, it slowly decomposes with the liberation of hydrogen chloride. It should not be stored for a long period in a tightly sealed container.

3. Methods of Preparation

Alkanesulfinyl chlorides have been prepared by the action of thionyl chloride on alkanesulfinic acids [3,4] and by the solvolysis of alkylsulfur trichlorides with water, alcohols, and organic acids.[5] The present procedure, which appears to be general for the preparation of sulfinyl chlorides in either the aliphatic or the aromatic series, is based on an improvement in the solvolysis method whereby the use of inert solvent is eliminated and the reaction is carried out in a one-phase system.[6]

4. Use of Methanesulfinyl Chloride

The utility of methanesulfinyl chloride lies in its great chemical reactivity. Through its ready hydrolysis, it serves as a convenient source of methanesulfinic acid. It reacts at low temperature with aromatic amines to form sulfinamides, and with alcohols to form sulfinate esters. When it is hydrolyzed in the presence of an equimolar quantity of sulfenyl chloride, a thiolsulfonate ester is produced.

[1] University of Maine, Orono, Maine.
[2] I. B. Douglass and B. S. Farah, J. Org. Chem., 24, 973 (1959).
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METHYLENECYCLOHEXANE

(Cyclohexane, methylene-)

$$(C_6H_5)_3P + CH_3Br \rightarrow [(C_6H_5)_3P{-}CH_3]Br \xrightarrow{C_4H_9Li}$$
$$(C_6H_5)_3P{=}CH_2$$

$(C_6H_5)_3P{=}CH_2 +$ ⬡$={=}O \rightarrow$ ⬡$={=}CH_2 + (C_6H_5)_3PO$
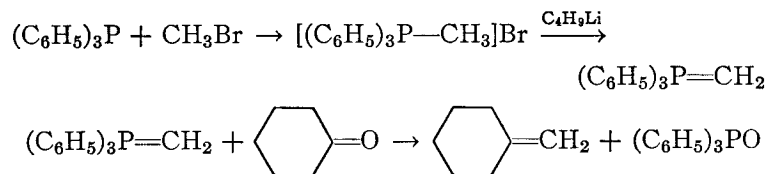
Submitted by George Wittig and U. Schoellkopf.[1]
Checked by John D. Roberts and Martin Vogel.

1. Procedure

A. *Triphenylmethylphosphonium bromide.* A solution of 55 g. (0.21 mole) of triphenylphosphine dissolved in 45 ml. of dry benzene is placed in a pressure bottle, the bottle is cooled in an ice-salt mixture, and 28 g. (0.29 mole) of previously condensed methyl bromide is added (Note 1). The bottle is sealed, allowed to stand at room temperature for 2 days, and is reopened. The white solid is collected by means of suction filtration with the aid of about 500 ml. of hot benzene and is dried in a vacuum oven at 100° over phosphorus pentoxide. The yield is 74 g. (99%), m.p. 232–233°.

B. *Methylenecyclohexane.* A 500-ml. three-necked round-bottomed flask is fitted with a reflux condenser, an addition funnel, a mechanical stirrer, and a gas inlet tube. A gentle flow of nitrogen through the apparatus is maintained throughout the reaction. An ethereal solution of *n*-butyllithium [2] (0.10 mole, about 100 ml., depending on the concentration of the solution) and 200 ml. of anhydrous ether is added to the flask. The solution is stirred and 35.7 g. (0.10 mole) of triphenylmethylphosphonium bromide is added cautiously over a 5-minute period (Note 2). The solution is stirred for 4 hours at room temperature (Note 3).

Freshly distilled cyclohexanone (10.8 g., 0.11 mole) is now added dropwise. The solution becomes colorless and a white precipitate separates. The mixture is heated under reflux overnight, allowed to cool to room temperature, and the precipitate

is removed by suction filtration. The precipitate is washed with 100 ml. of ether, and the combined ethereal filtrates are extracted with 100-ml. portions of water until neutral and then dried over calcium chloride. The ether is carefully distilled through an 80-cm. column packed with glass helices. Fractionation of the residue remaining after removal of the ether through an efficient, low-holdup column (Note 4) gives 3.4–3.8 g. (35–40%) of pure methylenecyclohexane, b.p. 99–101°/740 mm., n_D^{25} 1.4470 (Note 5).

2. Notes

1. Eastman Kodak Co. white label triphenylphosphine and Matheson Co. methyl bromide were used. Triphenylphosphine is available from the Metal and Thermit Corp., Rahway, New Jersey.

2. If the triphenylmethylphosphonium bromide is added too rapidly, the evolution of butane causes excessive frothing of the solution.

3. The small amount of precipitate in the orange solution is not unreacted starting material but triphenylphosphinemethylene.

4. The checkers used a 6 x 350 mm. spinning-band column with a total reflux variable take-off head. The band was spun at 1100 r.p.m.

5. The methylenecyclohexane was analyzed by vapor-phase chromatography and found to be better than 99% pure.

3. Methods of Preparation

The procedure is a modification of that published.[3] Methylenecyclohexane has been prepared by the pyrolysis of N,N-dimethyl-1-methylcyclohexylamine oxide, N,N,N-trimethyl-1-methylcyclohexylammonium hydroxide, N,N-dimethylcyclohexylmethylamine oxide, and N,N,N-trimethylcyclohexylmethylammonium hydroxide.[4] It has also been obtained from the pyrolysis of cyclohexylmethyl acetate [5] and of cyclohexylideneacetic acid [6] and from the dehydrohalogenation of cyclohexylmethyl iodide.[7]

[1] University of Heidelberg, Heidelberg, Germany.
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1-METHYLINDOLE

(Indole, 1-methyl-)
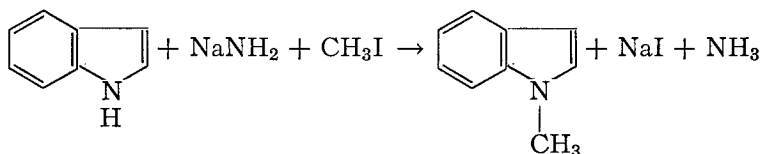
Submitted by K. T. Potts and J. E. Saxton.[1]
Checked by W. E. Parham, Wayland E. Noland, and
Bryce A. Cunningham.

1. Procedure

Caution! Ammonia gas is an extreme irritant and can cause serious burns to the eyes, etc. It is necessary to carry out the entire reaction under a well-ventilated hood.

In a 1-l. three-necked flask fitted with a motor stirrer (Note 1), gas inlet tube, dropping funnel, and a wide-bore soda-lime tube are placed 400–500 ml. of liquid ammonia and 0.1 g. of ferric nitrate nonahydrate (Note 2).

In small portions, just sufficient to maintain the blue color, 5.0 g. (0.22 gram atom) of clean, metallic sodium is added with vigorous stirring. After dissolution is complete (Note 3), a solution of 23.4 g. (0.20 mole) of indole (Note 4) in 50 ml. of anhydrous ether is added slowly and then, after an additional 10 minutes, a solution of 31.2 g. (0.22 mole) of methyl iodide in an equal volume of anhydrous ether is added dropwise. Stirring is continued for a further 15 minutes. The ammonia is allowed to evaporate (Note 5), 100 ml. of water is added, followed by 100

ml. of ether. The ether layer is separated, the aqueous phase extracted with an additional 20 ml. of ether, and the combined ether extracts washed with three 15 ml.-portions of water (Note 6) and dried over anhydrous sodium sulfate. The solvent is removed at atmospheric pressure, and the crude oil ($n_D^{18.5°}$ 1.6078) is purified by distillation under reduced pressure. 1-Methylindole is obtained as a colorless oil, b.p. 133°/26 mm., $n_D^{18.5°}$ 1.6082. In several runs the yield is 22.3–24.9 g. (85–95%).

2. Notes

1. Any sealed mechanical stirrer may be used. Those of the Hershberg[2] type were found particularly efficient during the formation of the sodium amide.

2. It was found most advantageous to run in the liquid ammonia from the commercial cylinder, laid on the floor with the foot raised slightly, and connected to the gas inlet tube with rubber tubing approximately 1 cm. in diameter. The large excess of liquid ammonia used obviates the need of a dry ice-acetone cooling bath and permits a reasonably rapid formation of sodium amide.

3. This occurs when the blue color has disappeared. The formation of the light gray sodium amide is usually complete within 20 minutes and may be observed by washing a portion of the outside of the flask with a little alcohol.

4. A commercial grade of indole is satisfactory.

5. The checkers removed the ammonia by distillation (water aspirator).

6. The checkers extracted with two 50-ml. portions of ether and three 50-ml. portions of water.

3. Methods of Preparation

1-Methylindole has been prepared from the *as*-methylphenylhydrazone of pyruvic acid,[3] by the action of sodium amide or sodium hydride on indole followed by methyl iodide at elevated temperatures,[4,5] by treatment of indole with methyl *p*-toluenesulfonate and anhydrous sodium carbonate in boiling xylene,[6] and by the action of methyl sulfate on indole previously treated

with sodium amide in liquid ammonia.[7] The present method is essentially that of Potts and Saxton.[8]

1-Methylindole has also been prepared by lithium aluminum hydride reduction of 1-methylindoxyl.[9] Compounds giving rise to NH absorption in the infrared (indole, skatole) can be completely removed[10] by refluxing the crude 1-methylindole over sodium for 2 days and then distilling the unreacted 1-methylindole from the sodio derivatives and tarry decomposition products.

[1] Department of Organic Chemistry, University of Adelaide, Adelaide, South Australia.

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2,6-NAPHTHALENEDICARBOXYLIC ACID
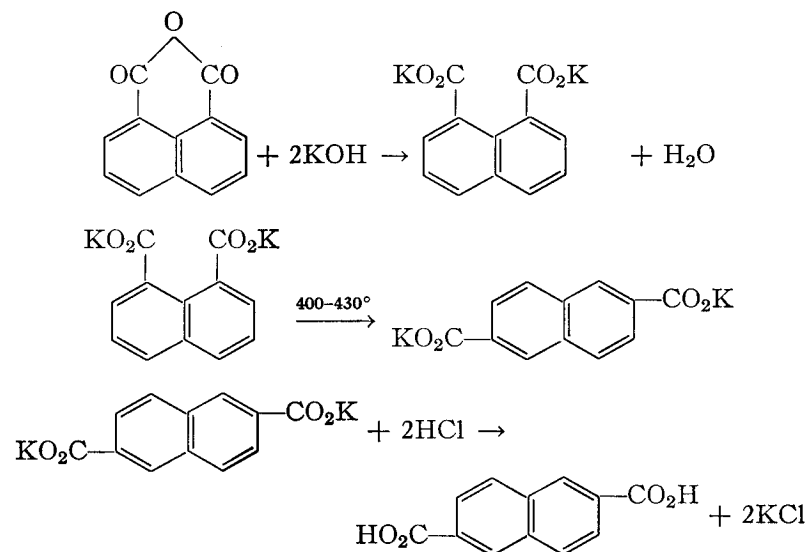
Submitted by BERNHARD RAECKE and HUBERT SCHIRP.[1]
Checked by B. C. McKUSICK and P. E. ALDRICH.

1. Procedure

A solution of 66.5 g. (1.01 moles) of 85% potassium hydroxide in 300 ml. of water in an 800-ml. beaker is heated to 60–70°, and 100 g. (0.505 mole) of commercial 1,8-naphthalic anhydride (Note 1) is stirred in. The pH of the resultant deep-brown solution is adjusted to a value of 7 (Note 2) with 6N hydrochloric acid and 3N potassium hydroxide. It is treated with 10 g. of decolorizing carbon and filtered. This operation is repeated. The filtrate is concentrated in a 1.5-l. beaker on a steam bath to about 180 ml. The concentrate is cooled to room temperature, 800 ml. of methanol is added with vigorous stirring by hand, and the mixture is cooled to 0–5°. The precipitated dipotassium naphthalate is separated by filtration, washed with 150 ml. of methanol, and dried in a vacuum oven at 150°/150 mm. The dried cream-colored salt weighs 130–135 g. (88–92%).

A mixture of 100 g. of dipotassium naphthalate and 4 g. of

anhydrous cadmium chloride [2] is ground in a ball mill for 4 hours. The mixture is placed in a 0.5-l. autoclave (Notes 3 and 4) that can be rocked, rolled, or shaken. The autoclave is evacuated, for oxygen lowers the yield of the product. The autoclave is then filled with carbon dioxide to a pressure of about 30 atm. The agitated autoclave is heated to an internal temperature of 400–430° in the course of 1–2 hours and is maintained at this temperature for 1.5 hours. The pressure rises to about 90 atm. in the course of the heating (Note 4).

The autoclave is cooled to room temperature, and the carbon dioxide is bled off. The solid reaction product is taken from the autoclave, pulverized, and dissolved in 1 l. of water at 50–60°. Ten grams of decolorizing carbon is added, and the mixture is stirred well and filtered to remove cadmium salts and carbon. The filtrate is heated to 80–90° and acidified with concentrated hydrochloric acid to pH 1 (Note 5). 2,6-Naphthalenedicarboxylic acid precipitates. It is separated from the hot mixture by filtration. It is then suspended in 500 ml. of water at 90–95° (Note 5), separated by filtration, and washed successively with 300 ml. of water, 300 ml. of 50% ethanol, and 300 ml. of 90% ethanol. After being dried at 100–150°/150 mm. in a vacuum oven, the 2,6-naphthalenedicarboxylic acid weighs 42–45 g. (57–61%). It decomposes on a heated block at 310–313°.

2. Notes

1. Suitable 1,8-naphthalic anhydride, m.p. 274–275°, is obtainable from Coaltar Chemicals Corp., 420 Lexington Ave., New York, N. Y.

2. Bromothymol blue or commercial universal indicator pH paper (graduated in 0.2-pH units) may be used as external indicators.

3. A 150-ml. shaking Hastelloy-C autoclave, manufactured by the Haynes Stellite Division of Union Carbide Co., Kokomo, Indiana, was used by the checkers. The approximate composition of the alloy is: Cr, 15.5–17.5%; Mo, 16–18%; Fe, 4.5–7%; W, 3.7–4.75%; and the remainder, Ni. Because their autoclave had only three-tenths the capacity of that used by the sub-

mitters, the checkers used three-tenths the quantities of materials given here.

4. The line to the pressure gauge tends to become clogged during the reaction.

5. Heat conduction in the heavy slurry that is formed is poor, and bumping may occur if the mixture is overheated. Efficient mechanical stirring aids this operation.

3. Methods of Preparation

2,6-Naphthalenedicarboxylic acid has been prepared by fusing dipotassium 2,6-naphthalenedisulfonate with potassium cyanide to give the corresponding dinitrile, which is hydrolyzed;[3] by oxidation of 2-methyl-6-acetylnaphthalene with dilute nitric acid at 200°;[4] by the thermal disproportionation of potassium α- or β-naphthoate to dipotassium 2,6-naphthalenedicarboxylate and naphthalene;[5] and by the present method.[6] The present method is much more convenient than earlier methods, if a suitable autoclave is available.

The present method for preparing aromatic dicarboxylic acids has been used to convert phthalic or isophthalic acid to terephthalic acid (90–95%); 2,2'-biphenyldicarboxylic acid to 4,4'-biphenyldicarboxylic acid; 3,4-pyrroledicarboxylic acid to 2,5-pyrroledicarboxylic acid; and 2,3-pyridinedicarboxylic acid to 2,5-pyridinedicarboxylic acid.[7] A closely related method for preparing aromatic dicarboxylic acids is the thermal disproportionation of the potassium salt of an aromatic monocarboxylic acid to an equimolar mixture of the corresponding aromatic hydrocarbon and the dipotassium salt of an aromatic dicarboxylic acid. The disproportionation method has been used to convert benzoic acid to terephthalic acid (90–95%); pyridinecarboxylic acids to 2,5-pyridinedicarboxylic acid (30–50%); 2-furoic acid to 2,5-furandicarboxylic acid; 2-thiophenecarboxylic acid to 2,5-thiophenedicarboxylic acid; and 2-quinolinecarboxylic acid to 2,4-quinolinedicarboxylic acid.[7] One or the other of these two methods is often the best way to make otherwise inaccessible aromatic dicarboxylic acids. The two methods were recently reviewed.[7]

[1] Paul-von-Hase Strasse 5, Dusseldorf 10, Germany.
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N-β-NAPHTHYLPIPERIDINE

(Piperidine, 1-(2-naphthyl)-)
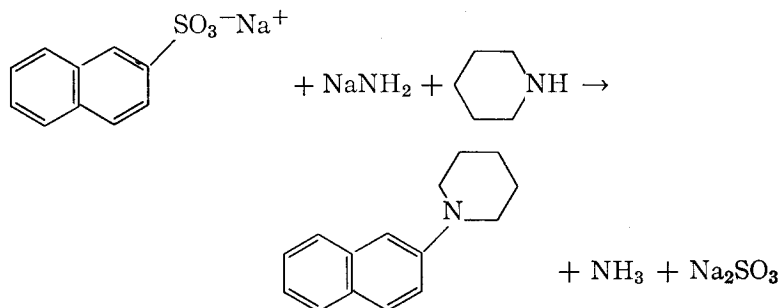
Submitted by J. F. Bunnett, T. K. Brotherton, and S. M. Williamson.[1]
Checked by Virgil Boekelheide and F. Lind.

1. Procedure

A dry 1-l. three-necked round-bottomed flask is fitted in the center neck with a sweep-blade stirrer whose shaft passes through an airtight bearing (Note 1). One side neck is fitted with a condenser topped by a soda-lime drying tube, and the other is fitted with a solid stopper. In the flask are placed 75 ml. of piperidine (Note 2) and 15.6 g. (0.4 mole) of sodium amide (Note 3), and the mixture is heated at reflux (Note 4) for 15 minutes with good stirring. The mixture is cooled just below reflux temperature, and 46 g. (0.2 mole) of sodium β-naphthalenesulfonate (Note 5) is added, followed by an additional 75 ml. of piperidine. The mixture is then heated at reflux for 12 hours with stirring.

To the cooled reaction mixture, 200 ml. of water is added carefully with stirring. Potassium carbonate is added with continued stirring until the water layer is saturated; the mixture is now transferred to a separatory funnel and extracted three times with 60-ml. portions of ether. The combined ether extracts are dried over solid sodium hydroxide and are then transferred to a simple distillation apparatus. Distillation is commenced with a steam bath as source of heat; when most of the ether has been removed, the steam bath is replaced by a flame. Distillation is continued until most of the piperidine (b.p. 106°) has been removed. The cooled residue in the distillation flask is recrystallized from petroleum ether (boiling range 30–60°) with the use of charcoal. There is obtained 30.0 g. (71%) of N-β-naphthylpiperidine as tan crystals, m.p. 52–56°. An additional recrystallization from the same solvent gives crystals, m.p. 56–58°, with about 10% loss in weight (Note 6).

2. Notes

1. The submitters used a ball-joint bearing. A mercury seal or a Trubore bearing should also suffice.

2. Commercial piperidine was purified by 6 hours' refluxing with sodium metal followed by distillation from sodium.

3. Sodium amide from Farchan Research Laboratories, Cleveland, Ohio, was used.

4. The submitters used an electric heating mantle as a source of heat.

5. Sodium β-naphthalenesulfonate, technical grade, from Matheson, Coleman and Bell was dried in an oven and then used directly.

6. The melting point of pure β-naphthylpiperidine is 58–58.5°.[2,3] By the same procedure the submitters have obtained N-phenylpiperidine (94%) from sodium benzenesulfonate and N-α-naphthylpiperidine (23%) from sodium α-naphthalenesulfonate.

3. Methods of Preparation

N-β-Naphthylpiperidine has been prepared by the condensation of β-bromonaphthalene [2,3] or of β-naphthol [4] with piperidine

at elevated temperatures; from the action of 1,5-dibromopentane on β-naphthylamine;[5] and from the action of the sodium amide-piperidine reagent on each of the eight monohalonaphthalenes [3,6] or on methyl β-naphthyl sulfone.[6] The present procedure is adapted from that of Brotherton and Bunnett.[7]

[1] Department of Chemistry, University of North Carolina, Chapel Hill, North Carolina.

[2] E. Lellman and M. Büttner, *Ber.*, **23**, 1383 (1890).

[3] J. F. Bunnett and T. K. Brotherton, *J. Am. Chem. Soc.*, **78**, 155 (1956).

[4] W. Roth, *Ber.*, **29**, 1175 (1896).

[5] M. Scholtz and E. Wassermann, *Ber.*, **40**, 856 (1907).

[6] J. F. Bunnett and T. K. Brotherton, *J. Am. Chem. Soc.*, **78**, 6265 (1956).

[7] T. K. Brotherton and J. F. Bunnett, *Chem. & Ind.* (London), **1957**, 60.

NEOPENTYL ALCOHOL

(2,2-Dimethyl-1-propanol)

$$(CH_3)_3CCH_2C(CH_3)=CH_2 + H_2O_2 \xrightarrow{H^+}$$

$$(CH_3)_3CCH_2C(CH_3)_2O_2H$$

$$(CH_3)_3CCH_2C(CH_3)_2O_2H \xrightarrow{H^+} (CH_3)_3CCH_2OH + CH_3COCH_3$$
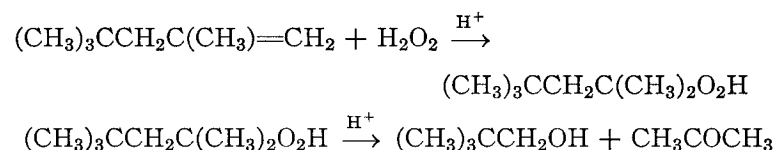
Submitted by Joseph Hoffman.[1]
Checked by John D. Roberts and J. Eric Nordlander.

1. Procedure

A. *Preparation of hydroperoxide.* In a 2-l. three-necked round-bottomed flask, equipped with a mechanical stirrer (Note 1), a dropping funnel, and a thermometer, is placed 800 g. of 30% hydrogen peroxide (Note 2). The flask is surrounded by an ice bath and rapid stirring is started. In the meantime, 800 g. of 95–96% sulfuric acid is added to 310 g. of cracked ice and the solution is cooled to 10°. When the temperature of the hydrogen peroxide reaches 5–10°, the cold sulfuric acid is added slowly from the dropping funnel during a period of about 20 minutes (Note 3). The temperature of the solution should not exceed 20° during the

addition. Commercial diisobutylene (224.4 g., 2 moles) is now added over a period of 5–10 minutes. The ice bath is removed and replaced by a water bath maintained at approximately 25° (Note 4). Vigorous agitation is maintained for 24 hours (Note 5). At the end of this time, mixing is discontinued, the mixture is transferred to a 2-l. separatory funnel and the two layers are allowed to separate (Note 6).

B. *Decomposition of hydroperoxide.* The upper organic layer (240–250 g.) is removed (Note 7) and added with vigorous stirring to 500 g. of 70% sulfuric acid in a 1-l. three-necked round-bottomed flask fitted with thermometer, stirrer, and dropping funnel and surrounded by an ice bath. The reaction temperature is maintained at 15–25° during addition, which requires 65–75 minutes (Note 8). Stirring is continued for 30 minutes at 5–10°, and then the reaction mixture is allowed to stand (0.5–3 hours) until the two layers are completely separated. The mixture is now transferred to a 1-l. separatory funnel and allowed to stand for about 15 minutes, after which time the lower layer is drawn off into 1 l. of water. The resulting mixture is distilled from a 3-l. flask without fractionation. The distillation is complete when 50-100 ml. of water has been collected (Note 9). The upper organic layer from the distillate (180–190 g.) is removed and dried over anhydrous magnesium sulfate (Note 10). The dried organic layer is filtered with the aid of a small amount of ether and distilled through an efficient fractionating column. The fraction which boils at 111–113° is collected (Notes 11 and 12). The yield is 60–70 g. (34–40% of theory, based upon the diisobutylene).

2. Notes

1. A heavy nichrome wire twisted into 4 loops (similar to an egg beater) was found to be very satisfactory. The two ends of the wire, extending several inches beyond the loops, were pushed into a piece of glass tubing for the stirrer shaft.

2. If the hydrogen peroxide is slightly below 30%, enough should be used to give the amount called for. The acid concentration should be maintained by increasing the sulfuric acid proportionately.

3. The hydrogen peroxide-sulfuric acid solution consists of approximately 12.5% hydrogen peroxide and 40% sulfuric acid.

4. Good results have been obtained in the temperature range 23–27°. Although the heat given off during the reaction is not great and is spread over a long period of time, the reaction vessel must nevertheless be surrounded by a water bath. If the room temperature is in the range indicated, no further regulation of the water bath temperature is required.

5. It is necessary to provide rapid and vigorous stirring in order to obtain good results.

6. The aqueous layer now contains approximately 8% hydrogen peroxide. This layer may be reused by adjusting the hydrogen peroxide percentage to 12.5 by use of either 30% or 50% hydrogen peroxide. The sulfuric acid must be readjusted to 40%. Approximately 1.9 kg. of aqueous layer is required for 2 moles of diisobutylene.

7. The submitter states that the procedure may be interrupted at this point by washing the organic layer free of acid with a saturated solution of sodium bicarbonate and that the hydroperoxide concentrate will keep for a long time, especially if refrigerated.

8. Care should be taken in decomposing the hydroperoxide. If the temperature is kept too low, decomposition takes place too slowly and hydroperoxide may accumulate. Heat is liberated during the decomposition, and after each small addition the temperature will rise. At the start, small amounts of hydroperoxide are added until the temperature rises above 15°; the rate is then adjusted to keep the temperature in the range 15–25°. The rise in temperature after each small addition is the best evidence that decomposition is actually taking place.

9. The submitter states that, when the distillation is essentially complete, there is a tendency for the residue to foam; this should be watched for and the heat should be turned back to avoid carryover into the distillate. The checkers did not experience any difficulties of this sort.

10. The checkers found that the commercial grade of "dried" magnesium sulfate was not completely effective and, even after three treatments with fresh drying agent, the subsequent distilla-

tion afforded an azeotrope of neopentyl alcohol and water of b.p. 80–85°. The organic layer of the azeotrope had to be separated from the water, dried, and redistilled to give the stated total yields.

11. The fraction between 95° and 110° should be taken off at a high reflux ratio; toward the end of the distillation the reflux ratio should again be increased. Most of the product comes over at 113°.

12. Pure neopentyl alcohol melts at about 55°. From time to time it will be necessary to circulate hot water through the take-off condenser in order to facilitate removal of the alcohol.

3. Methods of Preparation

Neopentyl alcohol has been made by lithium aluminum hydride reduction of trimethylacetic acid [2] and by treating tert-butyl-magnesium chloride with methyl formate.[3]

The preparation of neopentyl alcohol from diisobutylene herein described represents an example of acid-catalyzed addition of hydrogen peroxide to a branched olefin, followed by an acid-catalyzed rearrangement of the tertiary hydroperoxide formed. In addition to neopentyl alcohol, there are formed acetone and also small amounts of methanol and methyl neopentyl ketone by an alternative rearrangement of the hydroperoxide.

[1] Air Reduction Co., Murray Hill, New Jersey.

[2] R. F. Nystrom and W. G. Brown, J. Am. Chem. Soc., 69, 2548 (1947).

[3] L. H. Sommer, H. D. Blankman, and P. C. Miller, J. Am. Chem. Soc., 76, 803 (1954).

m-NITROPHENYL DISULFIDE

[Disulfide, bis-(m-nitrophenyl)]

$$2\ m\text{-}NO_2C_6H_4SO_2Cl + 10HI \rightarrow$$

$$(m\text{-}NO_2C_6H_4)_2S_2 + 5I_2 + 2HCl + 4H_2O$$
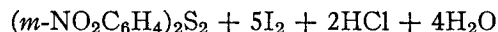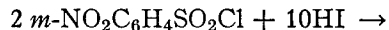
Submitted by W. A. Sheppard.[1]
Checked by John D. Roberts and W. H. Graham.

1. Procedure

A 5-l. three-necked round-bottomed flask equipped with a reflux condenser, a sealed mechanical stirrer, and a dropping funnel is set up in a hood and charged with 333 g. (1.50 moles) of m-nitrobenzenesulfonyl chloride (Note 1). The stirrer is started and 1033 ml. (7.5 moles) of 55–58% hydriodic acid (Note 2) is rapidly added dropwise over a period of 30–45 minutes (Note 3). After the addition is complete, the reaction mixture is stirred and refluxed on a steam bath for 3 hours. It is then cooled to room temperature, and the dropping funnel is replaced with an open powder funnel. Solid sodium bisulfite powder (Note 4) is added in portions until all the iodine has been reduced, and the reaction mixture is a suspension of pale yellow m-nitrophenyl disulfide in an almost colorless solution. The reaction mixture is filtered through a coarse-grade sintered-glass funnel to separate the disulfide, which is washed thoroughly with warm water to remove all inorganic salts. There is obtained 210–221 g. (91–96%) of crude m-nitrophenyl disulfide, m.p. 81–83°. This material is purified by dissolving it in approximately 800 ml. of boiling acetone, which is filtered hot and cooled to give 170–183 g. (74–79%) of the disulfide in the form of pale yellow prisms, m.p. 82–83°. By concentration of the mother liquor an additional 30–40 g. (13–17%) of disulfide, m.p. 82–83°, is obtained, so that the total yield of satisfactory product is 200–210 g. (86–91%).

2. Notes

1. Eastman Kodak white label m-nitrobenzenesulfonyl chloride was used.

2. Reagent grade hydriodic acid was generally employed, but material of lower purity may be used without decreasing the yield. The calculated amount of 45–47% hydriodic acid may also be employed [2] with only a slight diminution in yield.

3. The reaction of the hydriodic acid with m-nitrobenzenesulfonyl chloride is mildly exothermic, and iodine crystals precipitate as the reaction proceeds.

4. Approximately 3 lb. of sodium bisulfite is required to reduce the iodine. Technical grade bisulfite may be used satisfactorily. Caution should be observed in adding the bisulfite, since evolution of sulfur dioxide can cause excessive foaming. This foaming occurs a short time after each addition and is most noticeable when the iodine is almost neutralized. Iodine and product clinging to the upper walls of the flask and in the condenser may be conveniently rinsed into the reaction mixture with a stream of water from a wash bottle.

3. Methods of Preparation

The described method of preparation of m-nitrophenyl disulfide is essentially that of Foss and co-workers [2] and is a modification of that reported by Ekbom.[3] The disulfide has been prepared by reaction of potassium ethyl xanthate with m-nitrobenzenediazonium chloride solution, followed by hydrolysis to yield the mercaptan, which is subsequently oxidized with potassium ferrocyanide or dilute nitric acid to the disulfide.[4]

The usual method of preparing aromatic disulfides is to treat an aryl halide with Na_2S_2.[5] However, this method is limited to compounds where the halogen is strongly activated by electronegative groups (for example, o- or p-nitrochlorobenzene). The reaction of diazonium salts with xanthate is unsatisfactory for large-scale preparations because dilute solutions must be employed to reduce the hazard of explosion. Aromatic sulfonyl chlorides (not containing nitro groups) are also reduced with zinc and mineral acid to mercaptans,[6] which must be subsequently oxidized to the disulfide. The present method has been used to prepare nitronaphthalene disulfides,[7,8] naphthalene disulfide, and phenyl disulfide [8] and should be applicable to the preparation of

any symmetrical aromatic disulfides containing substituents stable to hydriodic acid.

4. Use of *m*-Nitrophenyl Disulfide

The disulfides are useful intermediates in the preparation of sulfenyl chlorides.[2,9]

[1] Contribution No. 515 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Inc., Wilmington, Delaware.

[2] N. E. Foss, J. J. Stehle, H. M. Shusett, and D. Hadburg, *J. Am. Chem. Soc.*, **60**, 2729 (1938).

[3] A. Ekbom, *Ber.*, **24**, 335 (1891).

[4] R. Leuckart and W. Holtzapfel, *J. prakt. chim.*, **41** (2), 197 (1890).

[5] *Org. Syntheses*, Coll. Vol. 1, 220 (1941).

[6] Th. Zinke and O. Krüger, *Ber.*, **45**, 3468 (1912).

[7] P. T. Cleve, *Ber.*, **20**, 1534 (1887).

[8] P. T. Cleve, *Ber.*, **21**, 1099 (1888).

[9] *Org. Syntheses*, Coll. Vol. 2, 1455 (1943).

N-PHTHALYL-L-β-PHENYLALANINE

(2-Isoindolineacetic acid, α-benzyl-1,3-dioxo-, L-)
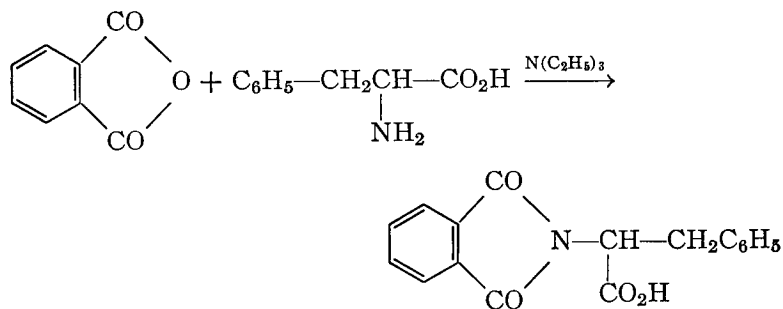
Submitted by AJAY K. BOSE.[1]
Checked by MAX TISHLER and GEORGE A. DOLDOURAS.

1. Procedure

In a 300-ml. flask fitted with a water separator and a reflux condenser are placed 16.5 g. (0.1 mole) of L-phenylalanine (Note

1), 14.8 g. (0.1 mole) of finely ground phthalic anhydride, 150 ml. of toluene, and 1.3 ml. of triethylamine. The flask is heated on an oil bath or with an electric mantle so as to maintain a vigorous reflux (Note 2). Separation of water is rapid at the beginning but becomes slower with time and is virtually over in 1.5 hours.

After 2 hours the water separator and the reflux condenser are disconnected, and volatile material is removed from the mixture under reduced pressure and on a steam bath (Note 3). The solid residue is stirred with 200 ml. of cold water and 2 ml. of hydrochloric acid until all the lumps are broken (Note 4).

The mixture is filtered under suction, and the product is washed with three 50-ml. portions of cold water. After drying in an air oven the product weighs 27–28 g. (91.5–95%) and consists of a white crystalline powder, m.p. 179–183°, $[\alpha]_D^{25}$ −198 to −200° (in alc.) (Note 5).

This product can be recrystallized by dissolving 10 g. in 20 ml. of hot ethyl alcohol (95%), adding 14 ml. of water, and allowing the solution to cool slowly so that no oiling out takes place. Colorless needles, m.p. 183–185°, $[\alpha]_D^{25}$ −211 to −217° (in alc.) (Note 6), are obtained (first crop, 7.5–8.5 g., 83–90% recovery; further quantities can be recovered from the mother liquor) (Note 7).

2. Notes

1. Material (supplied by Nutritional Biochemicals Corp., Cleveland, Ohio) of $[\alpha]_D^{25}$ −32° ($c = 1.98$ in water) was used.

2. An applicator stick (available from drug stores) can be used very conveniently to ensure smooth boiling. If a boiling chip is used, it should be colored (Carborundum, for example) to make its separation from the product convenient.

3. This evaporation during which a solid separates is very conveniently carried out in a rotary vacuum evaporator (manufactured by Rinco Instrument Co., Greenville, Illinois). An equally convenient alternative arrangement for solvent stripping that is in use in some laboratories is shown in Fig. 1. The splash-head A permits rapid removal of solvent under reduced pressure. Any solid carried beyond the flask B by spattering is arrested in A and can be washed down into B by introducing a low-boiling
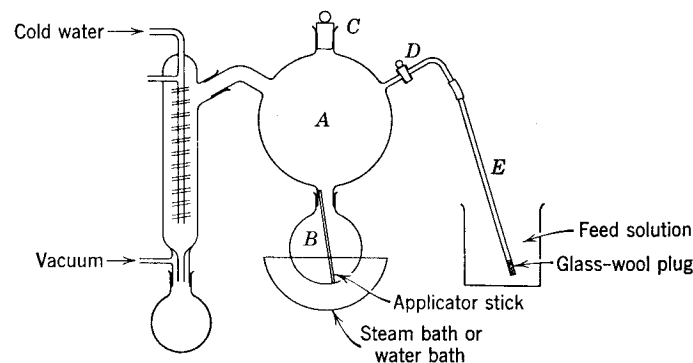
Fig. 1. Solvent stripper.

liquid like acetone through the port C. The side arm D permits continuous feeding into the "stripper." If the feed tube E is fitted with a plug of glass wool, the feed solution can be automatically filtered from suspended solids such as drying agents. Another advantage of this stripper is that a conveniently small collecting flask B can be used for a feed solution that is very dilute and large in volume.

4. The purity of the product depends largely on the efficient breaking up of all lumps and the subsequent washing.

5. This material gives satisfactory elemental analysis and can be used without purification for further reactions.

6. The checkers observed a rotation of -211 to $-217°$, as against -207 to $-212°$ reported by the submitter; Sheehan, Chapman, and Roth [2] report $-212°$.

7. The method described here can be applied to other amino acids and on a larger scale. Thus β-alanine on a 1.5-mole scale gave N-phthalyl-β-alanine in 96% yield and L-alanine gave N-phthalyl-L-alanine in 91% yield, and glycine ethyl ester hydrochloride (using more than one molar equivalent of triethylamine) gave the ethyl ester of N-phthalylglycine in 96% yield.

3. Methods of Preparation

N-Phthalyl-L-phenylalanine has been prepared by the fusion of L-alanine with phthalic anhydride.

The present method, based on a recent publication,[3] ensures a low temperature of reaction which precludes racemization and is more convenient than the fusion method for large-scale operation.

[1] Department of Chemistry, Stevens Institute, Hoboken, New Jersey.
[2] J. C. Sheehan, D. W. Chapman, and R. W. Roth, *J. Am. Chem. Soc.*, **74**, 3822 (1952).
[3] A. K. Bose, F. Greer, and C. C. Price, *J. Org. Chem.*, **23**, 1335 (1958).

p-QUINQUEPHENYL

$$p\text{-}ClCH_2C_6H_4CH_2Cl + 2(C_6H_5)_3P \rightarrow$$
$$p\text{-}(C_6H_5)_3P^+CH_2C_6H_4CH_2P^+(C_6H_5)_3; 2Cl^-$$

$$p\text{-}(C_6H_5)_3P^+CH_2C_6H_4CH_2P^+(C_6H_5)_3; 2Cl^-$$
$$+ 2C_6H_5CH{=}CHCHO + 2LiOC_2H_5 \rightarrow$$

$$+ 2(C_6H_5)_3PO + 2C_2H_5OH + 2LiCl$$

$$+ 2C_2H_5O_2CC{\equiv}CCO_2C_2H_5 \xrightarrow{OH^-} \xrightarrow{Fe(CN)_6^{3-}}$$
$$p\text{-}C_6H_5{-}C_6H_4{-}C_6H_4{-}C_6H_4{-}C_6H_5$$
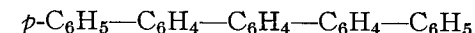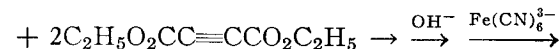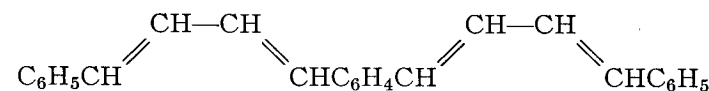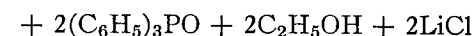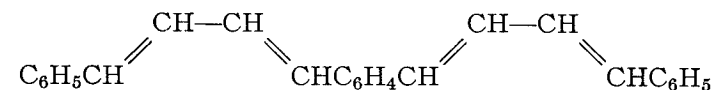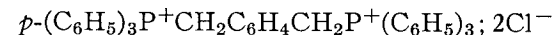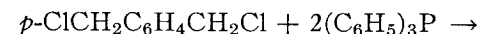
Submitted by Tod W. Campbell and Richard N. McDonald.[1]
Checked by Virgil Boekelheide and Richard E. Partch.

1. Procedure

A. *p-Xylylene-bis(triphenylphosphonium chloride)*. A mixture of 262 g. (1.0 mole) of triphenylphosphine (Note 1) and 84 g. (0.48 mole) of *p*-xylylene dichloride (Note 2) in 1 l. of dimethylformamide is heated at reflux with stirring for 3 hours (Note 3). The mixture is then allowed to cool to room temperature with stirring, and the white crystalline solid is collected, washed with 100 ml. of dimethylformamide followed by 300 ml. of ether, and

dried in a vacuum oven at 20 mm. pressure and 80°. The dry weight is 313–329 g. (93–98%).

B. *1,4-Bis-(4-phenylbutadienyl)benzene*. To a solution of 70 g. (0.10 mole) of *p*-xylylene-bis(triphenylphosphonium chloride) and 35 g. (0.26 mole) of cinnamaldehyde in 250 ml. of ethanol (Note 4) is added a solution of 0.25M lithium ethoxide in ethanol (Note 5). After being allowed to stand overnight at room temperature the yellow solid is collected by filtration, washed with 300 ml. of 60% ethanol, and dried in a vacuum oven at 20 mm. and 70°. The dry weight is 29–32 g. (87–95%). The solid is then dissolved in the minimum amount (about 2 l.) of boiling xylene, treated with decolorizing charcoal, and filtered. The filtrate is reduced in volume to about 1.2 l. and digested at the boiling point with a trace of iodine for 3 hours (Note 6). After the solution has stood overnight at room temperature, the yellow plates are collected by filtration, washed with benzene, and dried in a vacuum oven at 20 mm. pressure at 70°. The weight of crystals, m.p. 285–287° (Note 7), is 23–25 g. (69–75%).

C. *p-Quinquephenyl*. A mixture of 3.40 g. (0.020 mole) of diethyl acetylenedicarboxylate[2] and 3.34 g. (0.010 mole) of 1,4-bis-(4-phenylbutadienyl)benzene is refluxed with 20 ml. of *o*-dichlorobenzene for 3 hours. It is allowed to cool to about 80°, then 100 ml. of ethanol and 5 g. of potassium hydroxide are added, and the mixture is refluxed for about 2 hours. The solvent is evaporated on a steam bath under a nitrogen atmosphere (Note 8), and the damp solid is extracted with 200 ml. of water. The intense yellow or yellow-orange aqueous layer is filtered, then extracted twice with 75-ml. portions of ether, charcoal is added and then filtered to separate water-insoluble matter. The filtrate is just neutralized with dilute hydrochloric acid (Note 9) and then made basic with 5 g. of sodium carbonate. To this is added a solution of 30 g. of potassium ferricyanide in 200 ml. of water. The mixture rapidly becomes milky and is allowed to stand overnight (Note 10). The suspended solid is centrifuged and washed with water twice by centrifugation. It is dried in a vacuum oven to give 3.1–4.2 g. of a green-tinged solid (Note 11). The combined material from five runs (18 g.) is sublimed to give 10 g. (52%) of pure quinquephenyl, m.p.

385–390°. This can be recrystallized from dimethylsulfoxide to give well-defined leaflets.

2. Notes

1. Commercial triphenylphosphine was used without further purification.

2. A sample of this compound was obtained from Hooker Electrochemical Co. and used without further purification.

3. The salt begins to precipitate after about 30 minutes.

4. Commercial anhydrous ethanol was used throughout.

5. Prepared by dissolving 1.74 g. of lithium wire in 1 l. of ethanol.

6. After the volume is reduced, a small crystal of iodine is added whereupon large yellow leaflets of product begin to separate.

7. The product can be recrystallized readily from dimethylformamide to give yellow leaflets, m.p. 290–293°. However, it is pure enough to be used in the next step. This synthesis has also been applied to the preparation of 1,4-bis-[4-(*p*-tolyl)butadienyl]benzene (100%), 1,4-bis-[4-(3-nitrophenyl)butadienyl]benzene (56%), and 1,4-bis-(3-methyl-4-phenylbutadienyl)benzene (87%).

8. Nitrogen is used both for rapid removal of the solvent and to maintain an inert atmosphere.

9. The acid is added slowly with stirring until a trace of permanent precipitate is formed.

10. All the steps to this point can be completed in 1 day.

11. This procedure has been applied to the synthesis of 4,4'''' dimethylquinquephenyl and 2',3'''-dimethylquinquephenyl from 1,4-bis-[4-(*p*-tolyl)butadienyl]benzene and 1,4-bis-(3-methyl-4-phenylbutadienyl)benzene, respectively.

3. Methods of Preparation

1,4-Bis-(4-phenylbutadienyl)benzene has been obtained by condensation of cinnamaldehyde and *p*-phenylenediacetic acid with lead oxide.[3] *p*-Quinquephenyl has been prepared by the

reaction of biphenyllithium with 1,4-cyclohexanedione, followed by dehydration and air oxidation of the dihydroquinquephenyl;[4] by the Gatterman coupling reaction of benzenediazonium formate with copper;[5] by the Ullmann coupling of 4-iodoterphenyl and 4-iodobiphenyl with silver;[5] by the catalytic reduction of *p*-dibromobenzene;[6] and the Friedel-Crafts reaction of cyclohexene with terphenyl followed by dehydrogenation.[7] The procedure described represents the best route to both the 1,4-bis-(4-arylbutadienyl)benzenes and quinquephenyls that has been reported.[8]

[1] Pioneering Research Division, Textile Fibers Department, E. I. du Pont de Nemours and Co., Wilmington, Delaware.

[2] E. H. Huntress, T. E. Leslie, and J. Bornstein, *Org. Syntheses*, **32**, 55 (1952).

[3] G. Drefahl and G. Plotner, *Ber.*, **91**, 1274 (1958).

[4] E. Muller and T. Topel, *Ber.*, **72**, 273 (1939).

[5] O. Gerngross and M. Dunkel, *Ber.*, **57**, 739 (1924).

[6] M. Busch and W. Waber, *J. prakt. Chem.*, **146**, 1 (1936).

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2,2,5,5-TETRAMETHYLTETRAHYDRO-3-KETOFURAN

(3(2)-Furanone, 4,5-dihydro-2,2,5,5-tetramethyl-)
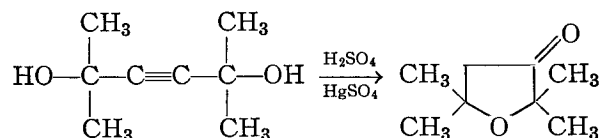
Submitted by MELVIN S. NEWMAN and WALTER R. REICHLE.[1]
Checked by VIRGIL BOEKELHEIDE and GRAHAM SOLOMONS.

1. Procedure

To the solution formed by dissolving 3 g. of mercuric oxide and 10 ml. of concentrated sulfuric acid (Note 1) in 1 l. of water is added 250 g. (1.76 moles) of 2,5-dimethyl-3-hexyne-2,5-diol (Note 2). The mixture is warmed with gentle swirling to dissolve the diol. At 80–90° the clear solution suddenly turns cloudy and the flask is immersed in a bath of water at about 20°. A colorless oil rises to the surface within a few minutes (Note 3).

The flask is then fitted for steam distillation, and 700–800 ml. of distillate is collected. After addition of 55 g. of sodium chloride to the distillate, the phases are separated in a 1-l. separatory funnel. The organic layer is dried by intermittent stirring with 25 g. of anhydrous magnesium sulfate for 6–10 hours.

The material is filtered and the residual solid washed twice with 50-ml. portions of low-boiling petroleum ether. The combined filtrates are concentrated and distilled through a short packed column to yield 190–205 g. (76–82%) of 2,2,5,5-tetramethyltetrahydro-3-ketofuran; b.p. 149–151°, n_D^{25} 1.4180.

2. Notes

1. Any other water-soluble mercury salt may be used.

2. Supplied by Air Reduction Chemical Company, 150 East 42nd Street, New York, N. Y.

3. The reaction is fairly exothermic. Cooling is advisable. An increase in acid and mercuric ion concentrations results in a faster reaction starting at a lower temperature.

3. Methods of Preparation

The procedure described is essentially that of Richet[2] which has been repeated.[3,4] The reaction is of interest since it provides a facile method of preparing tetrahydro-3-furanones which are useful reagents for alkylation in the Friedel-Crafts reaction.[4]

[1] Department of Chemistry, Ohio State University, Columbus, Ohio.

[2] M. Richet, *Ann. chim.*, **3** (12), 317 (1948).

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$\alpha,\alpha,\alpha',\alpha'$-TETRAMETHYLTETRAMETHYLENE GLYCOL

(2,5-Hexanediol, 2,5-dimethyl-)

$$\text{Fe}^{2+} + \text{H}_2\text{O}_2 \xrightarrow{\text{H}_2\text{SO}_4} \text{Fe}^{3+} + \text{OH}^- + \cdot\text{OH}$$

$$(\text{CH}_3)_3\text{COH} + \cdot\text{OH} \rightarrow \cdot\text{CH}_2 - \overset{\overset{\text{CH}_3}{|}}{\underset{\underset{\text{CH}_3}{|}}{\text{C}}} - \text{OH} + \text{H}_2\text{O}$$

$$2 \cdot\text{CH}_2 - \overset{\overset{\text{CH}_3}{|}}{\underset{\underset{\text{CH}_3}{|}}{\text{C}}} - \text{OH} \rightarrow \text{HO} - \overset{\overset{\text{CH}_3}{|}}{\underset{\underset{\text{CH}_3}{|}}{\text{C}}} - \text{CH}_2\text{CH}_2 - \overset{\overset{\text{CH}_3}{|}}{\underset{\underset{\text{CH}_3}{|}}{\text{C}}} - \text{OH}$$
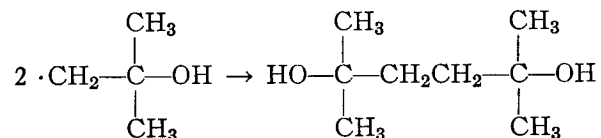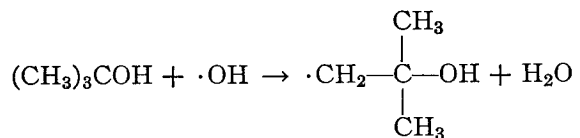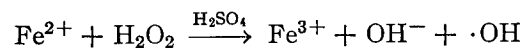
Submitted by E. L. JENNER.[1]
Checked by JOHN D. ROBERTS and M. PANAR.

1. Procedure

Tertiary butyl alcohol (900 ml., 702 g., 9.47 moles) is dissolved in a solution prepared by mixing 28 ml. (0.50 mole) of concentrated sulfuric acid with 1.5 l. of water in a 5-l. round-bottomed flask (Note 1) equipped with a thermometer, stirrer, gas inlet tube, and two addition burets. One buret is charged with 86 ml. (1 mole) of 11.6M hydrogen peroxide (Note 2), and the other with a solution of 278 g. (1 mole) of ferrous sulfate pentahydrate and 55.5 ml. (1 mole) of concentrated sulfuric acid in 570 ml. of water (Note 3). The reaction flask is swept out with nitrogen and cooled to 10° by means of an ice bath. Stirring is commenced and the two solutions are added simultaneously and equivalently over a period of 20 minutes. The temperature is held below 20°.

When the addition is completed, 50 ml. (1 mole) of 52% sodium hydroxide is added with stirring and cooling, and then 450 g. of anhydrous sodium sulfate (not all of the salt dissolves). The cold solution is transferred to a separatory funnel and the phases are separated. The organic layer is neutralized with 52% sodium hydroxide; approximately 20 ml. is required to bring the pH to 7. The aqueous layer, including the precipitated ferric hydroxide, is added to the aqueous portion of the reaction mixture and the whole is extracted with 400 ml. of t-butyl alcohol. This extract is similarly treated with 52% sodium hydroxide (about 5 ml. is required). The resulting aqueous layer is combined with the main aqueous fraction, which is again extracted with 400 ml. of t-butyl alcohol. This whole process is again repeated so that the organic phases comprise the three extracts and the phase which separated initially from the reaction mixture.

The four organic fractions are combined and distilled under reduced pressure. The distillation is continued until the temperature of the flask is about 70°/5 mm. in order to remove most of the t-butyl alcohol. The still residue is then extracted with 2 l. of ether and the extract is treated with decolorizing carbon and diatomaceous earth. Distillation of the ether at slightly reduced pressure from a water bath yields $\alpha,\alpha,\alpha',\alpha'$-tetramethyltetramethylene glycol as a pale yellow crystalline residue weighing 30–45 g. (41–62% yield based on hydrogen peroxide employed). The crude product is digested at room temperature in a mixture of 30 ml. of ether and 70 ml. of cyclohexane. The resulting slurry is filtered to yield 29–34 g. (40–46%; Note 4) of the glycol as a white crystalline solid, m.p. 87–88°. The product, which is pure enough for most purposes, can be further purified by recrystallization from ethyl acetate (1 g. in 4 ml.), cyclohexane (1 g. in 20 ml.), or water (1 g. in 2 ml.).

2. Notes

1. The flask should have creased sides and a conical indentation in the bottom and should be equipped with a high-speed, propeller-type stirrer rotated to force the liquid downwards. The stirrer should be constructed of glass because metals may interfere with the generation and utilization of the hydroxyl free radicals.

2. Commercial 35% hydrogen peroxide was employed. Any concentration from 5% to 50% may be used.

3. It is convenient to calibrate the burets so that the liquid is divided into 20 equal portions. Then, in the addition of the reagents, these calibrations aid in synchronizing the rates.

4. The submitter reports yields of 48–55%, which are slightly higher than those given here.

3. Methods of Preparation

$\alpha,\alpha,\alpha',\alpha'$-Tetramethyltetramethylene glycol has been prepared by the action of methylmagnesium bromide on acetonylacetone,[2-4] on ethyl levulinate,[5] and on ethyl succinate.[6,7] It has also been made by the hydrogenation of 2,5-dimethyl-3-hexyne-2,5-diol over nickel [8,9] and over platinum [10,11] and by the hydrogenation of 2,5-dihydroperoxy-2,5-dimethyl-3-hexyne.[12] Other methods of preparation include the autoxidation of 2,5-dimethylhexane [13] and the alkaline hydrolysis of 2,5-dibromo-2,5-dimethylhexane.[6] The present method, the hydroxyl- radical coupling of t-butyl alcohol,[14] is a one-step synthesis using readily available starting materials. A similar technique may be used to synthesize $\alpha,\alpha,\alpha',\alpha'$-tetramethyladipic acid from pivalic acid, $\alpha,\alpha,\alpha',\alpha'$-tetramethyltetramethylenediamine from t-butylamine, and $\alpha,\alpha,\alpha',\alpha'$-tetramethyladiponitrile from pivalonitrile.[14]

[1] Contribution No. 485 from Central Research Department, Experimental Station, E. I. du Pont de Nemours and Co., Wilmington, Delaware.

[2] E. Pace, *Atti accad. Lincei*, 7 (6), 760 (1928) [*C.A.*, 22, 3890 (1928)].

[3] R. Locquin and R. Heilmann, *Bull. soc. chim. France*, 45 (4), 1128 (1929).

[4] N. Zelinsky, *Ber.*, 35, 2139 (1902).

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[8] H. Adkins and D. C. England, *J. Am. Chem. Soc.*, 71, 2958 (1949).

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p-TOLUENESULFONYLHYDRAZIDE

(*p*-Toluenesulfonic acid, hydrazide)

$$\text{SO}_2\text{Cl} \quad\quad\quad\quad \text{SO}_2\text{NHNH}_2$$
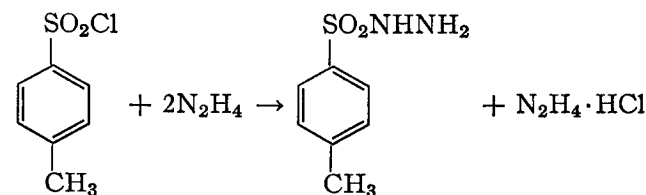
Submitted by Lester Friedman, Robert L. Litle,[1]
and Walter R. Reichle.
Checked by Max Tishler and Anthony N. Nutile.

1. Procedure

Into a 1-l. round-bottomed three-necked flask fitted with a thermometer, a mechanical stirrer, and a dropping funnel are placed 200 g. (1.05 moles) of *p*-toluenesulfonyl chloride and 340 ml. of tetrahydrofuran (Note 1). The stirred mixture is cooled in an acetone-ice bath to 10°; then a solution of hydrazine in water (135 ml. of 85% hydrazine hydrate, 2.22 moles; Note 2) is added at such a rate that the temperature is maintained between 10° and 15° (Note 3). Stirring is continued for 15 minutes after the addition is complete (Note 4). The reaction mixture is transferred to a separatory funnel. The lower layer is drawn off, and the upper tetrahydrofuran solution is washed with two 60-ml. portions of saturated, aqueous sodium chloride. The tetrahydrofuran layer is dried over anhydrous magnesium sulfate (20 g.) (Note 5), then filtered with suction through Celite (Note 6) and anhydrous magnesium sulfate. The filter cake is washed with 35 ml. of dry tetrahydrofuran (Note 1) to remove the absorbed hydrazide. The clear, combined filtrates (approximately 400 ml.) are transferred to a 2-l. flask and diluted with an equal volume of petroleum ether (b.p. 35–60°) while being vigorously agitated.

The *p*-toluenesulfonylhydrazide separates as fluffy, white plate-lets. The hydrazide, after cooling overnight in a refrigerator to complete crystallization, is filtered through a Büchner funnel. The filter cake is washed several times with petroleum ether (b.p. 35–60°), sucked dry, and then air-dried. *p*-Toluenesulfonyl-hydrazide (172–173 g., 90% yield) is obtained as a white, odorless, crystalline product, m.p. 101–104° (Note 7).

2. Notes

1. Commercial tetrahydrofuran (Matheson, Coleman and Bell) is washed several times with 40% aqueous sodium hydroxide to remove peroxides and organic stabilizers and then dried over solid sodium hydroxide. The clear supernatant liquid is used without further purification.

2. The submitters diluted 74 ml. of 95% hydrazine with 74 ml. of water. The dilution of hydrazine with water is exothermic. Hydrazine hydrate (50–100%) may be substituted if the volume of water is adjusted so that the resulting solution contains 50% hydrazine.

3. The addition is complete in 20–25 minutes.

4. During one run, 48 g. of product precipitated from the tetra-hydrofuran reaction mixture. This precipitate was filtered, washed with saturated, aqueous sodium chloride, water, and petroleum ether (b.p. 35–60°) to yield a crystalline product, m.p. 99–106°. For recovery of the remaining product, the tetrahydro-furan filtrate was worked up in accordance with the described procedure.

5. The tetrahydrofuran layer is dried overnight with stirring (magnetic stirrer).

6. Celite analytical filter aid, a product of the Johns-Manville Company, was used.

7. A purer product may be obtained by recrystallization. A solution of 20 g. of crude, dry *p*-toluenesulfonylhydrazide in 200 ml. of hot 50% aqueous methanol is cooled to 0° and the crystals are collected by filtration. The solid is washed once with 50 ml. of water and air-dried to yield 13 g. of *p*-toluenesulfonylhydra-zide, m.p. 104–107°.

A number of hydrazides have been prepared in comparable yields from their respective sulfonyl chlorides by the procedure above. These include *p*-bromobenzenesulfonylhydrazide, *p*-chlorobenzenesulfonylhydrazide, *p* - methoxybenzenesulfonylhy-drazide, *m*-nitrobenzenesulfonylhydrazide, *p*-nitrobenzenesulfon-ylhydrazide, *o*-nitrobenzenesulfonylhydrazide, benzenesulfonyl-hydrazide, and methanesulfonylhydrazide.

3. Methods of Preparation

p-Toluenesulfonylhydrazide has been prepared by shaking 50% hydrazine hydrate and *p*-toluenesulfonyl chloride in benzene for several hours.[2,3] Ammonia has been used as an agent for removing the hydrogen chloride evolved.[4]

4. Use of *p*-Toluenesulfonylhydrazide

On treatment with alkaline reagents, *p*-toluenesulfonylhydra-zones of aldehydes and ketones yield diazo compounds [5] which decompose in hydroxylic solvents to yield olefinic (or bicylic) compounds [6,7] and in aprotic solvents to yield olefins and cyclo-propanes.[8]

p-Toluenesulfonylhydrazide reacts with α-diketones to yield mono *p*-toluenesulfonylhydrazones which may be converted to α-diazoketones.[9]

[1] Department of Chemistry, Case Institute of Technology, Cleveland, Ohio.

[2] A. Albert and R. Royer, *J. Chem. Soc.*, **1949**, 1148.

[3] K. Freudenberg and F. Bluemmel, *Ann.*, **440**, 51 (1924).

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[5] W. R. Bamford and T. S. Stephens, *J. Chem. Soc.*, **1952**, 4735.

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2,4,5-TRIAMINONITROBENZENE

(1,2,4-Benzenetriamine, 5-nitro-)

m-dichlorobenzene (Cl, Cl) $+ 2KNO_3 + H_2SO_4 \rightarrow$

1,3-dinitro-4,6-dichlorobenzene (Cl, Cl, O_2N, NO_2) $+ K_2SO_4 + 2HOH$

(Cl, Cl, O_2N, NO_2) $+ 4NH_3 \xrightarrow[140°]{(CH_2OH)_2}$

(H_2N, NH_2, O_2N, NO_2) $+ 2NH_4Cl$

(H_2N, NH_2, O_2N, NO_2) $+ Na_2S_2 + HOH \rightarrow$

(H_2N, NH_2, O_2N, NH_2) $+ Na_2S_2O_3$
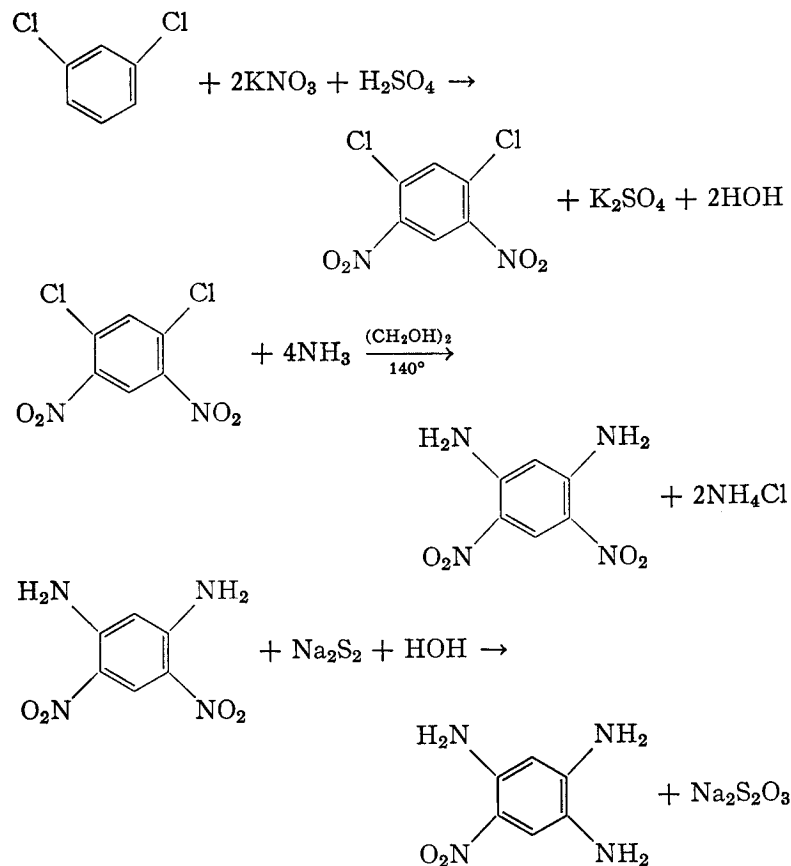
Submitted by J. H. Boyer and R. S. Buriks.[1]
Checked by James Cason and Taysir M. Jaouni.

1. Procedure

A. *1,3-Dinitro-4,6-dichlorobenzene* (*Caution!* Note 1). To a well-stirred solution of 140 g. (1.386 moles) of potassium nitrate in 500 ml. of concentrated sulfuric acid is added 100.0 g. (0.680 mole) of *m*-dichlorobenzene in one portion. The temperature of the reaction mixture rises during a few minutes to 135–140°, then

drops slowly to 125°. The stirred mixture is kept at 120–135° for an additional hour. After the reaction mixture has been cooled to about 90° it is poured over 1.5 kg. of crushed ice. The precipitated product is collected by suction filtration, drained well on the funnel, and dissolved in about 1 l. of boiling 95% ethanol. A small amount of insoluble impurity is removed by filtration of the hot solution by gravity through a fluted filter paper, and the product is allowed to crystallize in the refrigerator at about 0° (Note 2). The yield of yellow needles is 112–115 g. (70–71.5%), m.p. 103–104°.

B. *1,3-Dinitro-4,6-diaminobenzene.* Ammonia gas from a tank is bubbled into a well-stirred, clear yellow solution of 60.0 g. (0.253 mole) of 1,3-dinitro-4,6-dichlorobenzene in 400 ml. of technical grade ethylene glycol (heated to 140°), at such a rate that the gas is just absorbed. Within 30 minutes the color of the solution changes through orange to deep red. About 1 hour after the start of the reaction an orange, crystalline precipitate begins to separate. Heating is continued for an additional 2 hours as a slow stream of ammonia gas is bubbled through the reaction mixture. Finally, the reaction mixture is cooled to room temperature, the product is collected by suction filtration, and the finely divided orange-brown crystals are washed with boiling water and boiling ethanol. The yield of dried product, m.p. 300° (subl.), is 44–48 g. (88–95.5%) (Note 3).

C. *2,4,5-Triaminonitrobenzene.* A well-stirred slurry (Note 4) of 22.5 g. (0.114 mole) of 1,3-dinitro-4,6-diaminobenzene in 150 ml. of water is heated (Note 4) to the boiling point under reflux in a 500-ml. three-necked flask. To this vigorously stirred mixture, a clear orange-red solution of sodium polysulfide (prepared by heating a mixture of 30.0 g. of sodium sulfide nonahydrate, 7.25 g. of sulfur, and 125 g. of water) is added dropwise during a period of 1.5 hours. After completion of the addition, reflux of the well-stirred reaction mixture is maintained for an additional 1.5 hours. The resultant deep red mixture is cooled to 0° and the total insoluble material is collected by suction filtration. This residue of product, sulfur, and some starting material is thoroughly extracted with five 200-ml. portions of boiling water. The combined hot extracts are filtered by gravity and cooled to room

temperature to yield 9.5–10.0 g. (49.5–52%) of red needles, m.p. 200–207°, of 2,4,5-triaminonitrobenzene.

2. Notes

1. Unnecessary contact with dinitrodichlorobenzene should be avoided. It is a skin irritant and may cause severe blisters.

2. When a first crop of crystals was collected at room temperature and a second at 0°, the two lots exhibited the same melting point. When the filtrate from crystallization at 0° was concentrated to about 500 ml., the small crop of additional crystals had a much lower melting point.

3. The product is very slightly soluble in most solvents. It was used satisfactorily in the next step without further purification. Melting with sublimation occurs between 285° and 300°, depending on the rate of heating.

4. The submitters report that the best yield in this heterogeneous reaction depends upon particle size of the dinitrodiaminobenzene and efficient stirring, and that the diamine should be thoroughly ground in a mortar before use. The checkers found that grinding had no effect on the yield if heating was in an oil bath. Heating with a flame or heating mantle caused some caking and charring on the bottom of the flask, even with rather efficient stirring, and in one run the bottom of the flask dropped out during the reaction.

3. Methods of Preparation

1,3-Dinitro-4,6-dichlorobenzene has been prepared from *m*-dichlorobenzene and nitric acid[2] or potassium nitrate[3] in the presence of sulfuric acid. 1,3-Dinitro-4,6-diaminobenzene has been prepared by the nitration of *m*-bis-acetamidobenzene followed by hydrolysis;[4] or from 1,3-dinitro-4,6-dichlorobenzene and alcoholic ammonia in a pressure bottle at 150° for 8 hours.[2,5] The preparation and characterization of previously unknown 2,4,5-triaminonitrobenzene will be published elsewhere.

The present procedures represent simplified methods for obtaining the subject compounds and for accomplishing the illustrated conversions.

[1] Department of Chemistry, Tulane University, New Orleans, Louisiana.
[2] R. Nietzki and A. Schedler, *Ber.*, **30**, 1666 (1897).
[3] Footnote No. 7 in Th. Zincke, *Ann.*, **370**, 302 (1909) refers to this method used by Fries.
[4] R. Nietzki and E. Hagenbach, *Ber.*, **20**, 328, 2114 (1887).
[5] P. Ruggli and R. Fischer, *Helv. Chim. Acta*, **28**, 1270 (1945).

1,2,4-TRIAZOLE

(1H-1,2,4-Triazole)

(A) $NH_2NHCSNH_2$ + HCO_2H ⟶ $HCONHNHCSNH_2$ + H_2O

(B) $HCONHNHCSNH_2$ $\xrightarrow{\text{NaOH}}$

(C) $\xrightarrow{\text{HNO}_3}$
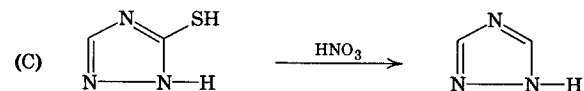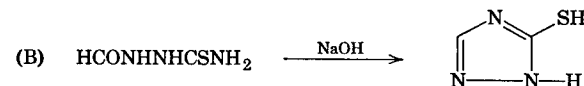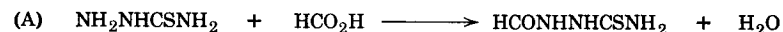
Submitted by C. Ainsworth.[1]
Checked by B. C. McKusick and B. C. Anderson.

1. Procedure

A. *1-Formyl-3-thiosemicarbazide.* Four hundred milliliters of 90% formic acid contained in a 2-l. round-bottomed flask is heated on a steam bath for 15 minutes, and then 182 g. (2 moles) of colorless thiosemicarbazide (Note 1) is added. The mixture is swirled until the thiosemicarbazide dissolves. The heating is continued for 30 minutes, during which time crystalline 1-formyl-3-thiosemicarbazide usually separates. Boiling water (600 ml.) is added, and the milky solution that results is filtered through a fluted filter paper. After standing for 1 hour, the filtrate is cooled in an ice bath for 2 hours, and the 1-formyl-3-thiosemicarbazide that separates is collected by suction filtration and air-dried overnight. It weighs 170–192 g. (71–81%) and melts at 177–178° with decomposition.

B. *1,2,4-Triazole-3(5)-thiol.* A solution of 178.5 g. (1.5 moles)

of 1-formyl-3-thiosemicarbazide and 60 g. (1.5 moles) of sodium hydroxide in 300 ml. of water in a 2-l. round-bottomed flask is heated on a steam bath for 1 hour. The solution is cooled for 30 minutes in an ice bath and then is treated with 150 ml. of concentrated hydrochloric acid. The reaction mixture is cooled in an ice bath for 2 hours, and the 1,2,4-triazole-3(5)-thiol that precipitates is collected by suction filtration. The thiol is dissolved in 300 ml. of boiling water and the solution is filtered through a fluted filter paper. The filtrate is cooled in an ice bath for 1 hour, and the thiol is collected by suction filtration and air-dried overnight. The 1,2,4-triazole-3(5)-thiol weighs 108–123 g. (72–81%) and melts at 220–222°.

C. *1,2,4-Triazole. Caution! This preparation should be carried out in a ventilated hood to avoid exposure to noxious fumes.*

A mixture of 300 ml. of water, 150 ml. of concentrated nitric acid, and 0.2 g. of sodium nitrite (Note 2) is placed in a 2-l. three-necked flask equipped with a stirrer and a thermometer. The stirred mixture is warmed to 45°, and 2 g. of 1,2,4-triazole-3(5)-thiol is added. When oxidation starts, as indicated by the evolution of brown fumes of nitrogen dioxide and a rise in temperature, a bath of cold water is placed under the reaction flask to provide cooling and an additional 99 g. (total, 101 g.; 1 mole) of 1,2,4-triazole-3(5)-thiol is added in small portions over the course of 30–60 minutes. The rate of addition and the extent of cooling by the water bath are so regulated as to keep the temperature close to 45–47° all during the addition. The water bath is kept cold by the occasional addition of ice.

When the addition is completed, the bath is removed and stirring is continued for 1 hour while the reaction mixture gradually cools to room temperature. Sodium carbonate (100 g.) is added in portions, followed by the cautious addition of 60 g. of sodium bicarbonate (Note 3). The water is removed from the slightly basic solution by heating the solution in a 3-l. round-bottomed flask under reduced pressure on a steam bath. To aid in removing the last traces of water, 250 ml. of ethanol is added to the residue and the mixture is heated under reduced pressure on a steam bath until it appears dry (Note 4).

The residue is extracted twice with 600 ml. of boiling ethanol

to separate the triazole from a large amount of inorganic salts. This extract is evaporated to dryness on a steam bath under reduced pressure, and the resulting residue is extracted with two 500-ml. portions of boiling ethyl acetate. The ethyl acetate extract is evaporated to dryness on a steam bath under reduced pressure. The crude 1,2,4-triazole remaining in the flask is dissolved by heating it with 50 ml. of absolute ethanol, and then 1 l. of benzene is added. The mixture is heated under reflux for 15 minutes, and the hot solution is filtered through a fluted filter paper. This extraction procedure is repeated. The two extracts are combined, cooled in an ice bath for 30 minutes, and filtered to remove colorless crystals of 1,2,4-triazole (m.p. 120–121°), weighing 28–30 g. after being dried in air. About 300 ml. of the filtrate is removed by slow distillation through a Claisen still-head to remove the bulk of the ethanol. The residual solution is cooled in an ice bath for 30 minutes and filtered to separate an additional 8–10 g. of colorless 1,2,4-triazole, m.p. 119–120°. The total weight of 1,2,4-triazole is 36–40 g. (52–58% yield).

2. Notes

1. The thiosemicarbazide must be of good quality or the yield and quality of 1-formyl-3-thiosemicarbazide will suffer. The thiosemicarbazide supplied by Olin Mathieson Chemical Corporation, obtained as a colorless free-flowing powder, can be used without purification.

2. The use of sodium nitrite helps to avoid an induction period.

3. A large flask is used to contain the vigorous effervescence that occurs upon the addition of carbonate. The final pH should be near 7.5, and it is reached after the addition of bicarbonate on longer causes bubbling.

4. Prolonged heating under reduced pressure should be avoided, since 1,2,4-triazole tends to sublime.

3. Methods of Preparation

1-Formyl-3-thiosemicarbazide has been prepared by the reaction of thiosemicarbazide and formic acid.[2]

1,2,4-Triazole-3(5)-thiol has been prepared by heating thio-semicarbazide and formic acid,[3] by heating 1-formyl-3-thiosemi-carbazide,[3] and by heating 1,3,5-triazine and thiosemicarbazide.[4] The ring closure of 1-formyl-3-thiosemicarbazide using aqueous base was suggested by L. F. Audrieth and F. Hersman.

1,2,4-Triazole has been prepared by the oxidation of substi-tuted 1,2,4-triazoles,[5] by the treatment of urazole with phos-phorus pentasulfide,[6] by heating equimolar quantities of formyl-hydrazine and formamide,[7] by removal of the amino function of 4-amino-1,2,4-triazole,[8] by oxidation of 1,2,4-triazole-3(5)-thiol with hydrogen peroxide,[3] by decarboxylation of 1,2,4-triazole-3(5)-carboxylic acid,[9] by heating hydrazine salts with form-amide,[10] by rapidly distilling hydrazine hydrate mixed with two molar equivalents of formamide,[11] by heating N,N'-diformyl-hydrazine with excess ammonia in an autoclave at 200° for 24 hours,[11] and by the reaction of 1,3,5-triazine and hydrazine monohydrochloride.[12]

Modifications of the present procedure for the preparation of 1,2,4-triazole have been used to prepare 3-aryl-1,2,4-triazoles[13] and 3-alkyl-1,2,4-triazoles.[14]

[1] The Lilly Research Laboratories, Indianapolis, Indiana.
[2] M. Freund and C. Meinecke, *Ber.*, **29**, 2511 (1896).
[3] M. Freund and C. Meinecke, *Ber.*, **29**, 2483 (1896).
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α,α,α-TRICHLOROACETANILIDE

(Acetanilide, α,α,α-trichloro-)
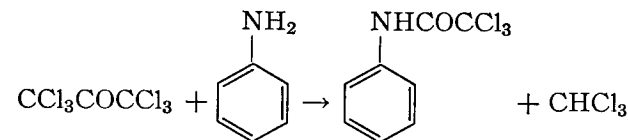
Submitted by BERNARD SUKORNICK.[1]
Checked by JOHN D. ROBERTS and EUGENE I. SNYDER.

1. Procedure

Into a 1-l. three-necked flask, fitted with a mechanical stirrer, a reflux condenser, a thermometer (Note 1), and a dropping funnel, is placed a solution of 265 g. (1 mole) of hexachloroacetone (Note 2) in 400 ml. of hexane (Note 3). To the stirred solution is added, dropwise, 93 g. (1 mole) of aniline (Note 4) over a period of 35–40 minutes. During this time the temperature rises to about 55°. After the addition is complete, stirring is continued at 65–70° for 45 minutes.

The hot solution is poured into a 1-l. beaker and cooled to 0–5°. The solid is collected on a filter and air-dried; it weighs 208–218 g. (87–91%) and melts at 90–92°. One recrystallization from 400 ml. of 90% ethanol (Note 5) yields 160–165 g. (67–69%) (Note 6) of product melting at 92.5–93.0° (Note 7). A second crop of 9–16 g. (4–7%), m.p. 93.5–95.5°, can be obtained by concentrating the filtrate to 200 ml. and cooling (Note 8).

2. Notes

1. The thermometer and the reflux condenser are fitted to a two-necked adapter.

2. Commercial hexachloroacetone (Allied Chemical Corpora-tion) was distilled and the fraction boiling at 93–97°/24 mm. was used.

3. Technical grade hexane suffices.

4. Technical grade aniline was purified by simple distillation and the light-yellow distillate was used directly.

5. The 90% ethanol was prepared by adding 22 ml. of water to 378 ml. of 95% ethanol.

6. The submitter reports a 76–81% yield of product melting at 94–96°.

7. The melting point is raised to 93.5–94.0° by carefully washing the product on a Büchner funnel with 50 ml. of iced 90% ethanol.

8. The submitter has applied this procedure successfully to several amines [2] (see Table I).

TABLE I

Amine	Yield of N-Trichloro-acetylamine, %	M.p., °C *
3-Chloroaniline	93	101
4-Chloroaniline	97	125–127
2-Toluidine	83	98
3-Toluidine	79	102–103
4-Toluidine	70	115
4-Fluoroaniline	83	96
Benzidine	65	301 (dec.)
Benzylamine	84	87–90
2-Phenylethylamine	97	117–120
Ammonia	96	141
Dimethylamine	89	b.p. 110–111°/16 mm.
2-Aminothiazole	80	196–198 (dec.)

* All melting points are uncorrected.

3. Methods of Preparation

Trichloroacetanilide has been prepared from hexachloroacetone and aniline,[3] from trichloroacetyl chloride and aniline,[4] by the action of aniline magnesium iodide on ethyl trichloroacetate,[5] by heating N-phenyltrichloroacetimidyl chloride with dilute methanol,[6] and from trichloroacetic acid and aniline in the presence of phosphorus oxychloride.[7]

[1] Allied Chemical Corp., P.O. Box 405, Morristown, New Jersey.
[2] Unpublished results.
[3] Ch. Cloez, *Ann. chim. phys.*, 9 (6), 204 (1886).
[4] W. E. Judson, *Ber.*, 3, 783 (1870).
[5] F. Bodroux, *Compt. rend.*, 140, 1598 (1905).
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[7] F. A. Berti and L. M. Ziti, *Arch. Pharm.*, 285, 372 (1952).

TRIPHENYLENE
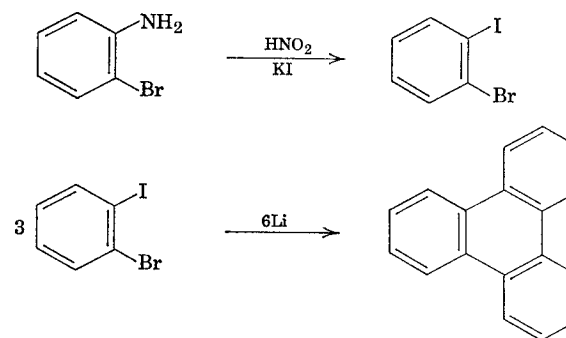
Submitted by H. Heaney and I. T. Millar.[1]
Checked by John D. Roberts and L. K. Montgomery.

1. Procedure

In a 600-ml. beaker fitted with a thermometer and mechanical stirrer are placed 150 ml. of concentrated hydrochloric acid and 55 g. (0.32 mole) of *o*-bromoaniline. After brief stirring, 100 g. of ice is added and the beaker is surrounded by an ice-salt bath. The solution is then diazotized by the dropwise addition with stirring of a solution of 24.3 g. (0.35 mole) of sodium nitrite in 100 ml. of water, the temperature being kept at 0–5°.

After stirring the diazotized solution for 15 minutes, it is slowly poured through a glass-wool filter into a solution of 180 g. (3.4 moles) of potassium iodide in 600 ml. of water. After standing overnight, the heavy dark oil is separated, washed successively with 10% aqueous sodium hydroxide, water, 5% aqueous sodium bisulfite and water, and then dried over magnesium sulfate.

Distillation under reduced pressure gives *o*-bromoiodobenzene as a nearly colorless liquid, b.p. 120–121° at 15 mm. Yield 65–75 g. (72–83%).

A 1-l. flask is fitted with a reflux condenser, dropping funnel, and a sealed mechanical stirrer. A nitrogen atmosphere is maintained in the flask during the entire reaction period.

In the flask is placed 150 ml. of anhydrous ether, and 5.7 g. (4.1 atomic equivalents) of lithium foil is then added (Note 1). A solution of 56.6 g. (0.2 mole) of o-bromoiodobenzene in 300 ml. of anhydrous ether is added dropwise (Note 2). When a vigorous reaction commences, the stirrer is started and the flask is cooled in ice water to maintain the temperature at about 10°. The reflux condenser is replaced by a thermometer, and the remainder of the o-bromoiodobenzene solution is added at a rate such that the temperature in the flask remains at about 10° (about 1.5 hours). When this addition is complete, 200 ml. of dry benzene is added; the mixture is stirred at 10° for 1 hour and finally at room temperature for 1 hour. The mixture is then poured through a glass-wool filter on 200 g. of ice.

The organic layer is separated, evaporated on a steam bath, and the dark semicrystalline residue is distilled with steam to remove biphenyl. The contents of the steam-distillation flask are then extracted with ether (Note 3), and the ethereal layer is separated, dried over magnesium sulfate, and percolated through a short column of chromatographic alumina (Notes 4 and 5). Evaporation of the ethereal solution gives crude triphenylene which is sublimed at 175–180° and 0.1 mm. pressure. After rejection of an initial sublimate of impure biphenyl, the sublimed material forms nearly colorless crystals, m.p. 186–194° (Note 6). Yield 8–9 g. (53–59%). It may be further purified by recrystallization from a mixture of methylene chloride and pentane yielding colorless crystals, m.p. 199° (Note 7).

2. Notes

1. Slugs of lithium, coated with paraffin oil, are hammered into thin foil. They are washed free of oil with dry ether and cut by scissors into slips which are allowed to fall directly into the ether in the reaction flask.

2. By adding 10–20 ml. of the o-bromoiodobenzene solution to the metal before stirring is started, high local concentrations of

the dihalo compound which initiate reaction are built up. An induction period of about 10 minutes is usually observed before the vigorous reaction commences.

3. The checkers found that, in view of the limited solubility of triphenylene in ether (about 1 g. per 100 ml.), care must be exercised in the extraction to ensure that all the product is removed.

4. The volume of ether solution must be reduced to approach the solubility limit of the triphenylene in ether before the chromatographic procedure.

5. The checkers used a 30-mm. (I.D.) chromatographic column charged with approximately 250 g. of activated (400° for 12 hours), acid-washed, chromatographic aluminum oxide (Merck and Co., Inc.).

6. The contaminant in the product of m.p. 186–194° is present in low concentration and is very probably o-terphenyl. It is characterized by an absorption near 695 cm.$^{-1}$ in the infrared which is absent in the spectrum of pure triphenylene.

The submitters report that the purity of the product is rather dependent upon the purity of the lithium used and that results can vary from batch to batch. In addition, they state that side reactions may be catalyzed by traces of heavy metals, that the degree of vigor in the initial reaction may influence the purity of the product owing to local overheating, and that increase in scale of this reaction is deleterious.

7. The checkers carried out this recrystallization by dissolving triphenylene in a minimum of methylene chloride maintained at reflux. Pentane was slowly added to this solution; up to 90% recovery was achieved.

3. Methods of Preparation

Triphenylene has been prepared by self-condensation of cyclohexanone using sulfuric acid [2] or polyphosphoric acid [3] followed by dehydrogenation of the product, dodecahydrotriphenylene, using copper,[2] palladium-charcoal,[3] or selenium;[4] by electrolytic oxidation of cyclohexanone;[5] from chlorobenzene and sodium [6] or phenyllithium;[7] from 2-cyclohexyl-1-phenylcyclohexanol [8] or

2-(1-cyclohexene-1-yl)-1-phenylcyclohexanol [3,9] by dehydrogenation; from 9-phenanthryl magnesium bromide and succinic anhydride followed by reduction, cyclization, and dehydrogenation; [10] and by the action of lithium on *o*-diiodobenzene. [11]

[1] University College of North Straffordshire, Keele, Straffordshire, England.

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SUBJECT INDEX

(This index comprises material from Volume 40 only; for previous volumes see Collective Volumes 1, 2, and 3 and Volume 39.

Names in small capital letters refer to the titles of individual preparations. A page number in boldface 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.

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AN ANNUAL PUBLICATION OF SATISFACTORY METHODS FOR THE PREPARATION OF ORGANIC CHEMICALS

VOLUME 40

1960

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CONTENTS