N-(*p*-ACETYLAMINOPHENYL)RHODANINE

[Rhodanine, 3-(*p*-acetamidophenyl)-]

$$CH_3CONH-\underset{}{\bigcirc}-NH_2 + (HO_2C-CH_2S)_2CS \xrightarrow{H_2O}$$

$$CH_3CONH-\underset{}{\bigcirc}-N\underset{S=C\quad CH_2}{\underset{\diagdown S \diagup}{|\qquad\quad|}}C=O + HSCH_2CO_2H$$
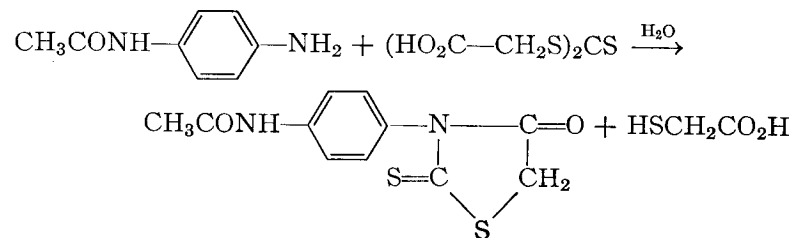
Submitted by R. E. Strube.[1]
Checked by John D. Roberts and Stanley L. Manatt.

1. Procedure

In a 2-l. round-bottomed flask fitted with a mechanical stirrer and a reflux condenser are placed 30.0 g. (0.20 mole) of *p*-aminoacetanilide (Note 1) and 400 ml. of water. The mixture is heated on a steam bath with stirring, and to the clear solution is added at once a hot solution of 45.2 g. (0.20 mole) of trithiocarbodiglycolic acid (Note 2) in 500 ml. of water. Heating and stirring are continued for 5 hours (Note 3). The steam bath is then replaced by an ice bath, and the reaction mixture is cooled to 20–25°. The precipitate is removed by suction filtration. The solid is transferred to a 500-ml. Erlenmeyer flask containing 200 ml. of water. The mixture is heated on the steam bath to 70–75° while the lumps are crushed by a glass rod to obtain a homogeneous mixture. The mixture is filtered with suction while hot, and the flask is cleaned by rinsing it with small amounts of hot water. The solid on the filter is sucked as dry as possible and then transferred to a 2-l. round-bottomed flask fitted with a reflux condenser. Glacial acetic acid (1.5 l.) is added and the mixture is heated in an oil bath to vigorous reflux for 5 minutes (Note 4). A small amount of solid does not dissolve, and this is removed by filtra-

tion while hot (Note 5). The filtrate is stirred mechanically and cooled to 15–20° by an ice bath and kept at this temperature for 1 hour. The slightly yellow crystals are collected by suction filtration, washed successively with 25 ml. of glacial acetic acid, 100 ml. of ethanol, and 100 ml. of ether. The yield of air-dried material is 26–28 g. (49–53% yield). The compound decomposes on heating above 240° (Note 6).

2. Notes

1. *p*-Aminoacetanilide (white label) supplied by Eastman Kodak Company was used.

2. Strube, *Org. Syntheses*, **39,** 77 (1959).

3. Within 10 minutes a precipitate is formed; the greater part of the reaction product is present after 2 hours' heating.

4. The purification should be carried out in a hood, since gas escapes during the heating and hot acetic acid is irritating to the eyes. The checkers used a 2-l. heating mantle instead of an oil bath.

5. The filtration of the hot acetic acid solution should be done with care. The flask was surrounded by a towel and rubber gloves were worn. The filtration can best be done in two steps. Approximately half of the hot acetic acid solution is filtered through a large, fluted filter paper; the other half is heated again to reflux and then filtered through another fluted filter paper. Filtration through a steam-heated Büchner funnel may sometimes be troublesome, since the suction accelerates crystallization causing plugging of the funnel stem.

6. Analytical values: Calcd. for $C_{11}H_{10}N_2O_2S_2$: C, 49.62; H, 3.78; N, 10.52; S, 24.08. Found: C, 49.76; H, 3.76; N, 10.36; S, 24.07.
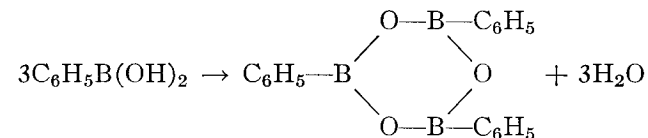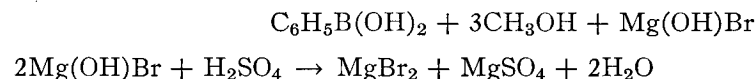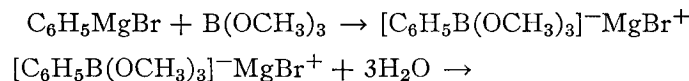
3. Methods of Preparation

This procedure is based on the method of Holmberg[2] for preparing N-substituted rhodanines. The synthesis of N-(*p*-acetylaminophenyl)rhodanine has not yet been reported in the literature.

[1] The Chemistry Department, The Upjohn Company, Kalamazoo, Michigan.
[2] Holmberg, *J. prakt. Chem.*, **81**, 451 (1910).

BENZENEBORONIC ANHYDRIDE

(Boroxine, triphenyl-)

$$C_6H_5MgBr + B(OCH_3)_3 \rightarrow [C_6H_5B(OCH_3)_3]^-MgBr^+$$

$$[C_6H_5B(OCH_3)_3]^-MgBr^+ + 3H_2O \rightarrow$$
$$C_6H_5B(OH)_2 + 3CH_3OH + Mg(OH)Br$$

$$2Mg(OH)Br + H_2SO_4 \rightarrow MgBr_2 + MgSO_4 + 2H_2O$$

$$3C_6H_5B(OH)_2 \rightarrow C_6H_5{-}B \underset{\diagdown O{-}B{-}C_6H_5}{\overset{\diagup O{-}B{-}C_6H_5}{\bigg\langle}} O \bigg\rangle + 3H_2O$$

Submitted by ROBERT M. WASHBURN, ERNEST LEVENS,
CHARLES F. ALBRIGHT, and FRANKLIN A. BILLIG.[1]
Checked by B. C. McKUSICK and H. C. MILLER.

1. Procedure

Caution! Benzeneboronic acid and its anhydride are toxic substances and may irritate mucous tissues such as those of the eyes. In case of contact, carefully wash exposed parts of the body with soap and water (Note 1).

The apparatus consists of a four-necked 5-l. round-bottomed Morton flask[2] fitted with a 500-ml. graduated dropping funnel with a pressure-equalizing side arm, a 1-l. graduated dropping funnel of the same type, a thermometer, an efficient mechanical stirrer (Note 2), and an inlet for dry nitrogen. The apparatus is thoroughly swept with dry nitrogen, and the reaction flask is charged with 1.5 l. of anhydrous ether, dry nitrogen (Note 3) being used for pressure transfer.

Three hundred thirty-six milliliters (312 g., 3.00 moles) of methyl borate is distilled directly into the 500-ml. dropping funnel shortly before starting the reaction (Note 4). One liter (544 g., 3.0 moles) of a 3*M* ethereal solution of phenylmagnesium bromide is pressure-transferred with dry nitrogen into the 1-l.

dropping funnel (Note 5). During subsequent operations until the hydrolysis step, a positive pressure of 10–20 mm. of nitrogen is maintained in the closed system by means of a mercury bubbler to prevent access of atmospheric moisture. The ether is cooled to below $-60°$ by a bath of Dry Ice and acetone and is kept below $-60°$ all during the reaction (Note 6). The reactants are added to the well-stirred reaction mixture alternately in small portions, first 10 ml. of methyl borate and then 30 ml. of phenylmagnesium bromide, the rate of addition being as rapid as is possible without the temperature of the mixture rising above $-60°$ (Note 7). Stirring is continued for an additional 20 minutes below $-60°$ after the addition of the reagents is completed.

The stirred mixture, maintained at or below $0°$, is hydrolyzed by the addition of 200 ml. of distilled water during 5 minutes. It is then neutralized by addition of a solution of 84 ml. of concentrated sulfuric acid in 1.7 l. of distilled water during 15 minutes. The mixture is transferred to a 5-l. separatory funnel, the ether layer is separated, and the aqueous layer is extracted with three 250-ml. portions of ether.

The combined ether layer and extracts are transferred to a 5-l. round-bottomed flask equipped with a Hershberg stirrer,[3] a dropping funnel, a Claisen head with a water-cooled condenser, an electric heating mantle, and an ice-cooled receiver (Note 8). After approximately one-half of the ether has been removed by distillation from the stirred mixture, 1.5 l. of distilled water is added slowly while the distillation is continued until a head temperature of $100°$ is reached (Note 9).

While stirring is continued, the aqueous distilland is cooled in an ice bath (Note 10). The benzeneboronic acid, which separates as small white crystals, is collected on a Büchner funnel and washed with petroleum ether. The petroleum ether removes traces of dibenzeneborinic acid, which are seen in the hot mother liquor as globules of brown oil and which may color the product. The acid is dehydrated to benzeneboronic anhydride by heating it in an oven at $110°$ and atmospheric pressure for 6 hours (Note 11). Benzeneboronic anhydride is obtained as a colorless solid, weight 240–247 g. (77–79%) (Note 12), m.p. 214–216°.

2. Notes

1. A summary of the physiological activity of benzeneboronic acid may be found in reference 4a.

2. The submitters found that for a preparation of this size a 1-inch Duplex Dispersator (Premier Mill Corp., Geneva, New York) operating at 7500 r.p.m. provided excellent agitation of the heterogeneous reaction mixture. For smaller preparations (1-l. flask) they found that a Stir-O-Vac (Labline, Inc., 217 N. Desplainer St., Chicago 6, Illinois) operating at 5000 r.p.m. was satisfactory. The type of agitation is very important for, whereas the submitters obtained yields of around 91%, the checkers obtained yields of only 77–80% with either a Morton stirrer [2] (excessive splashing deposited some of the reaction mixture on the warm upper walls of the flask) or a Polytron dispersion mill type of stirrer (there was too much hold-up in the stirrer housing).

3. Tank nitrogen was dried with phosphorus pentoxide.

4. Methyl borate (b.p. 68°) forms a 1:1 azeotrope (b.p. 54.6°) with methanol (b.p. 64°).[5] Since the presence of even a small amount of methanol reduces the yield considerably more than would be expected from the stoichiometry,[4,6] methyl borate stocks should be freshly distilled through a good column to remove as fore-run any methyl borate-methanol azeotrope which may have been formed by hydrolysis during storage.

5. Mallinckrodt analytical reagent grade ether, dried over sodium, was used. The methyl borate was the commercial product of American Potash and Chemical Corporation containing 99% ester as received. The phenylmagnesium bromide was purchased as a $3.0M$ solution in ether from Arapahoe Special Products, Inc., Boulder, Colorado.

6. The yield of benzeneboronic anhydride is highly dependent upon the reaction temperature, as the following data of the submitters show. At a reaction temperature of $15°$ the yield was 49%; at $0°$, 76%; $-15°$, 86%; $-30°$, 92%; $-45°$, 92%; $-60°$, 99%. The yields are based on the combined first and second crops of benzeneboronic acid.

7. At a given temperature, the maximum yield of benzeneboronic acid and the minimum amount of by-product dibenzene-

borinic acid are obtained when neither reagent is present in excess. The addition of small increments of reactants is a convenient approximation imposed by the difficulty of adjusting stopcocks to small rates of flow. Alternatively, the Hershberg dropping funnel[7] or other metering device may be used to maintain the stoichiometry. Addition times, which depend upon the efficiency of stirring and heat transfer, vary from about 1 hour at $-60°$ to 15 minutes at $0°$.

8. Stirring is helpful during the ether distillation to prevent superheating.

9. Small amounts of benzene, phenol, and biphenyl, which may be formed in the reaction, are removed by the steam distillation. Enough water has been added to ensure solution of all of the product.

10. The product crystallizes at $43°$ with a temperature rise to $45°$. The solubility of benzeneboronic acid in water (g./100 g. of water) is approximately 1.1 at $0°$ and 2.5 at $25°$; the solubility-temperature relationship is linear to at least $45°$.

11. If benzeneboronic acid rather than its anhydride is desired, it can be obtained by air-drying the moist acid in a slow stream of air nearly saturated with water. The yield of acid is 282–332 g. One can readily convert the anhydride to the acid by recrystallizing it from water. Benzeneboronic acid gradually dehydrates to the anhydride if left open to the atmosphere at room temperature and 30–40% relative humidity. The melting point observed is that of the anhydride because the acid dehydrates before it melts.

12. The submitters report a yield of 91% and state that an additional 27 g. (9%) of acid can be obtained from the aqueous mother liquor.

3. Methods of Preparation

The procedure described[4] is a modification of the method of Khotinsky and Melamed,[8] who first reported the preparation of boronic acids from Grignard reagents and borate esters. Benzeneboronic acid and the corresponding anhydride also have been prepared by reaction of phenylmagnesium bromide with boron

trifluoride,[9] by reaction of phenyllithium with butyl borate,[10] and by reaction of diphenylmercury with boron trichloride.[11]

The present procedure is also applicable to the synthesis of substituted benzeneboronic acids.[4a] Benzeneboronic acid and its anhydride are of use as starting materials for the synthesis of phenylboron dichloride[12] and of various substituted boronic and borinic acids and esters.[6,13]

[1] American Potash and Chemical Corporation, Whittier, California.

[2] Morton, *Ind. Eng. Chem., Anal. Ed.*, **11**, 170 (1939); Morton and Redman, *Ind. Eng. Chem.*, **40**, 1190 (1948).

[3] Pinkney, *Org. Syntheses*, Coll. Vol. **2**, 117 (1943).

[4] (a) Washburn, Levens, Albright, Billig, and Cernak, presented before the Division of Industrial and Engineering Chemistry, *131st National Meeting, American Chemical Society*, Miami, April 8, 1957, *Abstracts of Papers*, p. 12L; (b) Washburn, Billig, Bloom, Albright, and Levens, presented before the Division of Inorganic Chemistry, *133rd National Meeting, American Chemical Society*, San Francisco, April 18, 1958, *Abstracts of Papers*, pp. 45L–46L.

[5] Schlesinger, Brown, Mayfield, and Gilbreath, *J. Am. Chem. Soc.*, **75**, 213 (1953).

[6] Seaman and Johnson, *J. Am. Chem. Soc.*, **53**, 711 (1931).

[7] Hershberg, *Org. Syntheses*, Coll. Vol. **2**, 129 (1943).

[8] Khotinsky and Melamed, *Ber.*, **42**, 3090 (1909).

[9] Krause and Nitsche, *Ber.*, **55B**, 1261 (1922); Krause, German Patent 371,467 (1923) [*C.A.*, **18**, 992 (1924)].

[10] Brindley, Gerrard, and Lappert, *J. Chem. Soc.*, **1955**, 2956.

[11] Michaelis and Becker, *Ber.*, **15**, 180 (1882).

[12] Dandegaonker, Gerrard, and Lappert, *J. Chem. Soc.*, **1957**, 2893.

[13] Lappert, *Chem. Revs.*, **56**, 987, 1013 (1956).

2,5-DIAMINO-3,4-DICYANOTHIOPHENE

(3,4-Thiophenedicarbonitrile, 2,5-diamino-)

$$(NC)_2C{=}C(CN)_2 + 2H_2S \xrightarrow{\text{Pyridine}} \underset{H_2N}{\overset{NC}{\bigsqcup}}\underset{S}{\overset{CN}{\bigsqcup}}NH_2 + S$$
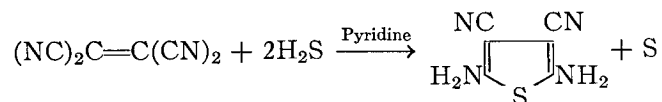
Submitted by W. J. Middleton.[1]
Checked by James Cason and Ralph J. Fessenden.

1. Procedure

Caution! Since carbon disulfide is highly flammable and hydrogen sulfide highly toxic, this reaction should be carried out in a hood, with due precaution against fire. It is also recommended that tetracyanoethylene not be allowed to come into contact with the skin.

A 1-l. three-necked flask is fitted with a sealed mechanical stirrer, a condenser protected by a drying tube, a thermometer, and an inlet tube extending to the bottom of the flask. A solution of 25.6 g. (0.2 mole) of recrystallized tetracyanoethylene[2] in 300 ml. of acetone is placed in the flask, and 300 ml. of carbon disulfide is added. The flask and its contents are cooled to 0° by means of a salt-ice bath. With good stirring, hydrogen sulfide is passed into the reaction mixture at a moderate rate while the temperature is maintained at 0–5°. The solution becomes milky after a few minutes owing to the formation of colloidal sulfur. The hydrogen sulfide addition is continued for about 30 minutes, or until the solution is thoroughly saturated.

The hydrogen sulfide addition is temporarily suspended, and 100 ml. of pyridine is added rapidly in one portion through the condenser as the solution is stirred vigorously (Note 1). The solution becomes clear, and then 2,5-diamino-3,4-dicyanothiophene begins to precipitate immediately. The hydrogen sulfide addition is resumed and is continued for about 30 minutes while the temperature of the reaction mixture is maintained at 0–5°. Finally, the reaction mixture is stirred for an additional 30 minutes at 0–5°, then the yellow precipitate of the thiophene is collected on a Büchner funnel, thoroughly washed with about 500 ml. of acetone, and dried in the air or in a vacuum desiccator. The yield of crude product of yellow or buff color amounts to 30–31 g. (92–95%).

This material is sufficiently pure for most purposes. If a purer product is desired, the crude material is dissolved in 300 ml. of dimethylformamide, 10 g. of activated alumina (48–100 mesh) is added, and the mixture is filtered. The filtrate is heated to 80–90° on a steam bath, then 1 l. of boiling water is added immediately (Note 2). The resultant mixture is cooled in an ice bath, and the light buff crystals of 2,5-diamino-3,4-dicyanothiophene that separate are collected on a Büchner funnel and thoroughly washed with 500 ml. of acetone; weight 26–28 g. (79–85%). The product has no definite melting point but sublimes with some decomposition when heated above 250°.

2. Notes

1. Unless the pyridine is added quite rapidly, some of the product will begin to precipitate before all of the sulfur has dissolved, and the final product will be contaminated with sulfur.

2. This operation should be carried out as rapidly as possible, since prolonged heating in dimethylformamide results in loss of product.

3. Methods of Preparation

2,5-Diamino-3,4-dicyanothiophene has been prepared only by the action of hydrogen sulfide or sodium sulfide on tetracyanoethylene or tetracyanoethane.[3] Unlike most aminothiophenes, 2,5-diamino-3,4-dicyanothiophene is very stable and can be stored indefinitely. Its amino groups show the normal reactivity of aromatic amines. For example, they readily condense with aromatic aldehydes to form highly colored bis-anils.[3] Hot 10% sodium hydroxide rearranges 2,5-diamino-3,4-dicyanothiophene to 2-amino-3,4-dicyano-5-mercaptopyrrole.[3]

[1] Contribution No. 483 from Central Research Department, Experimental Station, E. I. du Pont de Nemours & Co. (Inc.), Wilmington, Delaware.

[2] Carboni, *Org. Syntheses*, **39**, 64 (1959).

[3] Middleton, Englehardt, and Fisher, *J. Am. Chem. Soc.*, **80**, 2822 (1958).

DI-*n*-BUTYLDIVINYLTIN

(Tin, dibutyldivinyl-)

$$CH_2\!\!=\!\!CHBr + Mg \xrightarrow{\text{Tetrahydrofuran}} CH_2\!\!=\!\!CHMgBr$$

$$2CH_2\!\!=\!\!CHMgBr + (n\text{-}C_4H_9)_2SnCl_2 \rightarrow$$
$$(n\text{-}C_4H_9)_2Sn(CH\!\!=\!\!CH_2)_2 + MgCl_2 + MgBr_2$$
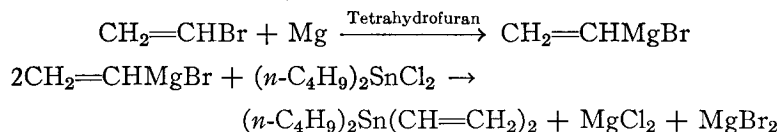
Submitted by DIETMAR SEYFERTH.[1]
Checked by MELVIN S. NEWMAN and S. RAMACHANDRAN.

1. Procedure

In a 2-l. three-necked flask, equipped with a Dry Ice-acetone reflux condenser, a mechanical stirrer, and a 250-ml. dropping funnel, is placed 29.2 g. (1.2 g.-atoms) of magnesium turnings. Enough tetrahydrofuran (THF) (Note 1) to cover the magnesium is added, stirring is begun, and about 5 ml. of vinyl bromide (Note 2) is added. After the reaction has started (Note 3), an additional 350 ml. of the THF is added. The rest of the vinyl bromide (140 g., 1.3 moles, total), dissolved in 120 ml. of THF, is added at such a rate that a moderate reflux is maintained. After the addition has been completed, the solution is refluxed for 30 minutes (Note 4). The Grignard solution is then cooled to room temperature, and the Dry Ice-acetone condenser is replaced with a water condenser which is fitted with a Drierite-filled drying tube. A solution of 135 g. (0.44 mole) of di-*n*-butyltin dichloride (Note 5) in 250 ml. of THF (Note 6) is then added, with stirring, at such a rate that a moderate reflux is maintained. After the addition has been completed, the reaction mixture is refluxed for 20 hours. The mixture is then cooled to room temperature and is hydrolyzed by the slow addition of 150 ml. of a saturated ammonium chloride solution (Note 7). The organic layer is then decanted and the residual salts are washed thoroughly with 3 portions of ether, the washings being added to the organic layer. The ether and the THF are stripped off at atmospheric pressure;

a Claisen distillation head is used. The residue is then distilled at reduced pressure using a vacuum-jacketed Vigreux column equipped with a total-reflux partial take-off head to give 95–116 g. (74–91%) of di-*n*-butyldivinyltin, b.p. 60° at 0.4 mm., n_D^{25} 1.4797 (Notes 8 and 9).

2. Notes

1. Tetrahydrofuran, obtained from the Electrochemicals Department of E. I. du Pont de Nemours & Co. (Inc.), was distilled from lithium aluminum hydride prior to use. It is not advisable to leave THF purified in this manner standing around for longer periods, since, in the absence of the inhibitor present in the commercial material, peroxides form fairly rapidly. (See also p. 57; Note 2).

2. Vinyl bromide, obtained from the Matheson Company, was redistilled prior to use. The distillate was collected in a receiver cooled with a Dry Ice-acetone mixture and protected from daylight.

3. In most cases the formation of the Grignard reagent began in the absence of any initiator. In cases where the reaction did not begin within a few minutes, 0.5 ml. of methyl iodide served to initiate attack on the magnesium.

4. In small-scale preparations of vinylmagnesium bromide it is advisable to carry out the reaction in an atmosphere of dry nitrogen in order to prevent hydrolysis and oxidation of the Grignard reagent. In larger-scale preparations such as the one described here, where a considerable excess of Grignard reagent is used, such precautions are not necessary.

5. Di-*n*-butyltin dichloride is a commercial product of Metal and Thermit Corporation, Rahway, New Jersey.

6. The checkers found that 250 ml. of dry ether was equally effective.

7. Enough saturated ammonium chloride solution is added to cause coagulation of the inorganic salts to a particle size of about 2 5 mm. in diameter; the volume of solution required varies but averages about 100–120 ml. per mole of Grignard reagent. If the hydrolysis is stopped at this point, a clear, essentially dry organic

layer results, and in most instances no further drying is required before distillation.

8. This general procedure has been used to prepare [2,3] a large number of vinyltin compounds, including:

$$CH_2\!\!=\!\!CHSnR_3 \qquad (R = CH_3,\ C_2H_5,\ n\text{-}C_3H_7,\ n\text{-}C_4H_9,\ C_6H_5)$$

$$(CH_2\!\!=\!\!CH)_2SnR_2 \quad (R = CH_3,\ n\text{-}C_4H_9,\ (CH_3)_3SiCH_2,\ C_6H_5)$$

$$(CH_2\!\!=\!\!CH)_3SnR \quad (R = n\text{-}C_4H_9,\ C_6H_5)$$

$$(CH_2\!\!=\!\!CH)_4Sn$$
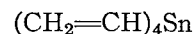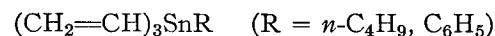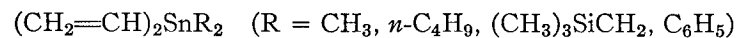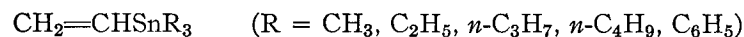
9. Grignard reagents other than vinylmagnesium bromide may be used in this general procedure. The initial use of a Dry Ice-acetone condenser, is then not required. Use of the THF solvent provides a distinct advantage over the method recently described in detail [4] in which ether is used as a solvent, since fewer steps are required.

3. Methods of Preparation

The above procedure is essentially that described previously by the author.[2] Di-*n*-butylvinyltin has been prepared by the reaction between vinylmagnesium chloride with either di-*n*-butyltin dichloride or di-*n*-butyltin oxide.[5] The preparation of vinyl-magnesium bromide was first described by Normant.[6]

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

[2] Seyferth and Stone, *J. Am. Chem. Soc.*, **79**, 515 (1957).

[3] Seyferth, *J. Am. Chem. Soc.*, **79**, 2133 (1957).

[4] Van der Kerk and Luijten, *Org. Syntheses*, **36**, 86 (1956).

[5] Rosenberg, Gibbons, and Ramsden, *J. Am. Chem. Soc.*, **79**, 2137 (1957).

[6] Normant, *Compt. rend.*, **239**, 1510 (1954).

DICYANOKETENE ETHYLENE ACETAL

(1,3-Dioxolane-$\Delta^{2,\alpha}$-malononitrile)
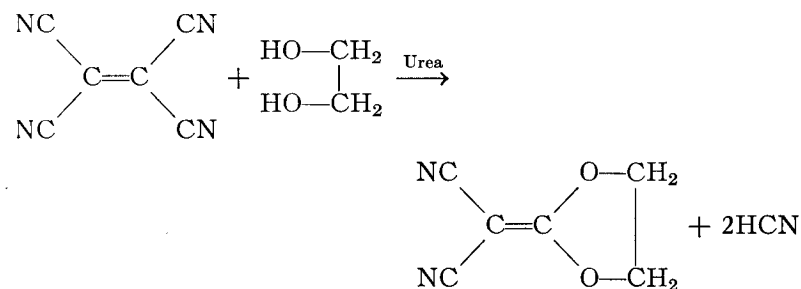
Submitted by C. L. Dickinson and L. R. Melby.[1]
Checked by James Cason, Edwin R. Harris, and William T. Miller.

1. Procedure

Caution! This preparation must be carried out in a good hood because hydrogen cyanide is evolved. It is inadvisable to allow contact of tetracyanoethylene with the skin.

Urea (4.0 g., 0.067 mole) is dissolved in 50 ml. of distilled ethylene glycol (Note 1) contained in a 125-ml. Erlenmeyer flask. Finely divided recrystallized tetracyanoethylene [2] (25.6 g., 0.20 mole) is added, and the flask is heated on a steam bath at 70–75° with frequent stirring by hand with a thermometer until solution is complete (about 15 minutes). The resultant brownish-yellow solution is then cooled in ice water, and the precipitated dicyanoketene ethylene acetal is collected on a Büchner funnel. The acetal is first washed with two 25-ml. portions of cold ethylene glycol and then washed thoroughly with cold water to remove the ethylene glycol. The dicyanoketene ethylene acetal, which may be dried in air or in a vacuum desiccator, is obtained in the form of large slightly pink needles, m.p. 115–116.5° (Note 2); yield 21–23 g. (77–85%).

2. Notes

1. Moisture in the ethylene glycol leads to lowered yields. Satisfactory results are obtained with glycol collected at 199.5–201° from a simple distillation.

2. The color may be removed by recrystallization from ethanol after treatment with decolorizing carbon; however, the melting point is not improved and occasionally is found to be lowered.

3. Methods of Preparation

The synthesis of dicyanoketene ethylene acetal described here is a slight modification of one published recently.[3] The procedure has been applied successfully to the synthesis of dicyanoketene dimethyl acetal and dicyanoketene diethyl acetal.[3]

Dicyanoketene ethylene acetal reacts with tertiary amines to give quaternary ammonium inner salts.[3] Similarly, it reacts with sulfides to give sulfonium inner salts.[3] These products are generally solids that can be used to characterize tertiary amines and sulfides. Dicyanoketene acetals can be converted to pyrimidines, pyrazoles, or isoxazoles in one step.[4]

[1] Contribution No. 481 from Central Research Department; Experimental Station, E. I. du Pont de Nemours & Co. (Inc.), Wilmington, Delaware.

[2] Carboni, *Org. Syntheses*, **39**, 64 (1959).

[3] Middleton and Engelhardt, *J. Am. Chem. Soc.*, **80**, 2788 (1958).

[4] Middleton and Engelhardt, *J. Am. Chem. Soc.*, **80**, 2829 (1958).

9,10-DIHYDROXYSTEARIC ACID

(low-melting isomer)

(Octadecanoic acid, 9,10-dihydroxy-)

$$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H + H_2O_2 + HCO_2H \rightarrow$$

Oleic acid

$$CH_3(CH_2)_7\underset{OH}{CH}{-}\underset{OCHO}{CH}(CH_2)_7CO_2H$$

$$CH_3(CH_2)_7\underset{OH}{CH}{-}\underset{OCHO}{CH}(CH_2)_7CO_2H + 2NaOH \rightarrow$$

$$CH_3(CH_2)_7\underset{OH}{CH}{-}\underset{OH}{CH}(CH_2)_7CO_2Na + HCO_2Na$$

$$CH_3(CH_2)_7\underset{OH}{CH}{-}\underset{OH}{CH}(CH_2)_7CO_2Na + HCl \rightarrow$$

$$CH_3(CH_2)_7\underset{OH}{CH}{-}\underset{OH}{CH}(CH_2)_7CO_2H + NaCl$$

Low-melting isomer

Submitted by DANIEL SWERN, JOHN T. SCANLAN, and GERALDINE B. DICKEL.[1]

Checked by JOHN D. ROBERTS and EDGAR F. KIEFER.

1. Procedure

To a well-stirred mixture of 141 g. (0.5 mole) of oleic acid (Note 1) and 425 ml. of formic acid (Note 2) in a 1-l. three-necked flask at 25° is added the appropriate amount (Note 3) of 30% (100 volume) hydrogen peroxide (approximately 60 g.) over a 15 minute period (Note 4). The reaction becomes mildly exothermic after a lag of about 5–10 minutes, and homogeneous after about 20–30 minutes. The temperature is maintained at 40° with a cold water bath at the beginning, and with a warm water bath or heating mantle toward the end, of the reaction.

After about 3 hours or after analysis has indicated that the peroxide has been consumed (Note 5), the formic acid is removed by distillation under reduced pressure (b.p. 50°/125 mm.) in a stream of gas (carbon dioxide or nitrogen) to prevent bumping (Note 6). The residue in the flask, which consists of hydroxy-formoxystearic acids, is heated for 1 hour at 100° with an excess of 3N aqueous sodium hydroxide, and the hot, amber-colored soap solution is cautiously poured into an excess of 3N hydrochloric acid with stirring. The oil which separates is allowed to solidify, and the aqueous layer is discarded. The tan-colored solid is remelted on the steam bath by addition of hot water and stirred well to remove residual salts and water-soluble acids (Note 7). When the oil has solidified, the aqueous layer is discarded, and the solid is broken into small pieces and dissolved in 400 ml. of 95% ethanol by heating on the steam bath. After crystallization at 0° for several hours, the product is collected on a filter and dried under vacuum. The yield of crude 9,10-dihydroxystearic acid is 75–80 g., m.p. 85–90°. After a second recrystallization from 250 ml. of 95% ethanol, the product weighs about 60–65 g. and melts at about 90–92°. A third recrystallization may be necessary to produce a pure product melting at 94–95°. The over-all yield is 55–60 g. (50–55%, based on the available oleic acid) (Note 8).

2. Notes

1. The checkers used commercial u.s.p. oleic acid, which has an iodine number of about 60–70 and contains 65–75% oleic acid. The submitters report that, if highly purified oleic acid is used, the yield of fairly pure 9,10-dihydroxystearic acid is almost quantitative, but the purification procedure for oleic acid [*Biochem. Preparations*, **2**, 100 (1952)] is more lengthy and inconvenient than the purification of the hydroxylation product. The over-all yield is approximately the same in either case.

2. The formic acid employed is the 98–100% grade. The submitters report that the 90% grade of acid is satisfactory, but the reaction mixture remains heterogeneous throughout. They also state that, instead of formic acid, an equal volume of glacial

acetic acid containing 2.5% by weight of concentrated sulfuric acid may be employed. With acetic acid-sulfuric acid, a 6-hour reaction time is required. However, the yield of 9,10-dihydroxystearic acid is slightly lower than the yield obtained when formic acid is employed and the iodine number of the crude reaction product is about 6–9.

3. If commercial oleic acid is used, the iodine number should be determined beforehand and the quantity of hydrogen peroxide adjusted accordingly. The hydrogen peroxide should be assayed immediately before use; "100 volume peroxide" usually contains about 30% hydrogen peroxide by weight. This determination is conveniently carried out by weighing 0.2–0.3 g. of the hydrogen peroxide solution into an Erlenmeyer flask with a ground-glass stopper and adding 20 ml. of a glacial acetic acid-chloroform solution (3:2 by volume). Two milliliters of saturated aqueous potassium iodide solution is added, and the mixture is allowed to stand for 5 minutes. Distilled water (75 ml.) is added and the liberated iodine titrated with 0.1N sodium thiosulfate solution to a starch end point. This procedure is also satisfactory for determining the peroxide content of the oxidation mixture, except that 1–2 g. samples are taken [cf. Wheeler, *Oil & Soap*, **9**, 89 (1932)].

4. The submitters state that in one-tenth scale preparations the hydrogen peroxide solution can be added in 1 portion. In larger runs the addition may require 30 minutes to 1 hour.

5. The reaction time ranges from 1.5 to about 4 hours. Progress of the reaction should be followed by determining the peroxide content of the oxidation mixture at half-hour intervals after all the hydrogen peroxide has been added. Approximately all the peroxide should be consumed before distillation is attempted.

6. Instead of removing the formic acid by distillation, the reaction mixture may be poured into a large quantity of water and the oily layer dissolved in ether. The ether solution is washed free of formic acid and then subjected to distillation to remove the ether; hydroxyformoxystearic acids are left as a residue. The submitters found that, in larger-scale operations (five or more times the size of the run described), no ether was

required and the oily layer was washed with water until free of formic acid. When acetic acid containing sulfuric acid was employed as the solvent, the reaction mixture was poured into hot water, and the oil which formed was separated mechanically or by extraction with ether.

7. The pH of the wash water should be below 6 in order to be certain that all soap in the product has been converted to free acid. If the pH is above 6, a small quantity of $3N$ hydrochloric acid should be added and the stirring continued for several minutes.

8. The submitters report that the high-melting isomer of 9,10-dihydroxystearic acid can be prepared from elaidic acid [*Biochem. Preparations*, **3**, 118 (1953)] by essentially the procedure described for oleic acid. With elaidic acid, instead of removing the formic acid by distillation, the reaction mixture may be poured into hot water and the oil which forms separated mechanically. The product is not readily soluble in ether. When acetic acid containing sulfuric acid is employed as the solvent, the reaction mixture is poured into *hot* water with thorough mixing, allowed to cool to room temperature, and filtered. The subsequent procedure (saponification and acidification) is the same as that described for the hydroxylation of oleic acid except that the crude dihydroxystearic acid, obtained after acidification of the soap, cannot be melted with hot water during the washing but is merely stirred well at 95–100° on the steam bath with a large quantity of hot water (Note 7). About 5 ml. of ethanol per gram of solute should be used in the recrystallization. The pure product melts at 130–131°. The yield depends on the purity of the starting material; if highly purified elaidic acid is used, the yield is about 80% after one recrystallization.

3. Methods of Preparation

The procedures described have been published.[2] Other procedures, which are not so satisfactory as the ones described, have also been published.[3,4]

[1] U. S. Dept. of Agriculture, Eastern Utilization Research and Development Division, Philadelphia 18, Pennsylvania.

[2] Swern, Billen, Findley, and Scanlan, *J. Am. Chem. Soc.*, **67**, 1786 (1945).
[3] Hilditch, *J. Chem. Soc.*, **1926**, 1828; Hilditch and Lea, *ibid.*, **1928**, 1576.
[4] Scanlan and Swern, *J. Am. Chem. Soc.*, **62**, 2305 (1940).
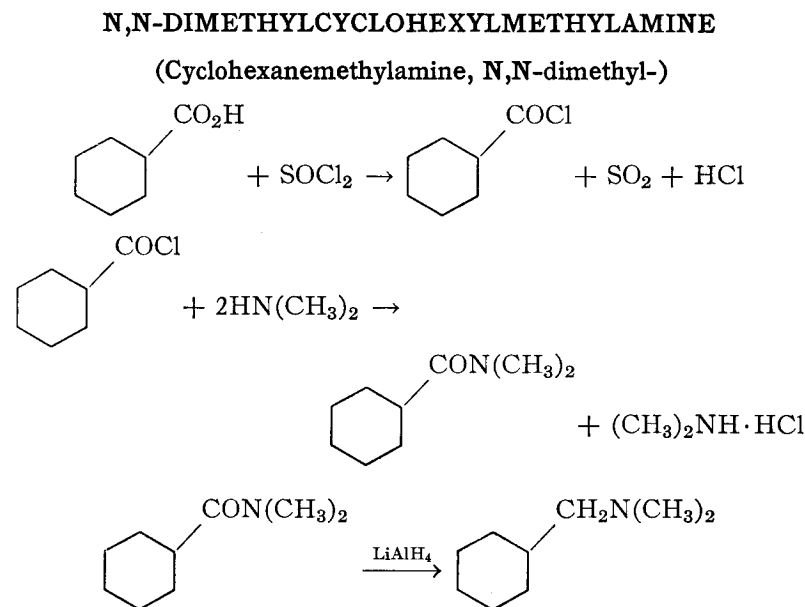
N,N-DIMETHYLCYCLOHEXYLMETHYLAMINE

(Cyclohexanemethylamine, N,N-dimethyl-)

Submitted by ARTHUR C. COPE and ENGELBERT CIGANEK.[1]
Checked by WILLIAM E. PARHAM and ROBERT KONCOS.

1. Procedure

A. *N,N-Dimethylcyclohexanecarboxamide.* In a 1-l. three-necked flask equipped with a reflux condenser and a dropping funnel, both carrying drying tubes, is placed 128 g. (1.0 mole) of cyclohexanecarboxylic acid (Note 1). Thionyl chloride (179 g., 1.5 moles) (Note 1) is added during 5 minutes to the acid, with stirring by a magnetic stirrer. The flask is placed in an oil bath and heated at a bath temperature of 150° for 1 hour. The reflux condenser is then replaced by a distillation head (Note 2), 200 ml. of anhydrous benzene is added, and the mixture is distilled until

the temperature of the vapors reaches 95°. The mixture is cooled, another 200 ml. of anhydrous benzene is added, and the distillation is continued until the temperature of the vapors again reaches 95°. The cooled residual acid chloride is transferred with a little benzene to a dropping funnel which is attached to a 2-l. three-necked flask. The flask is fitted with an efficient mechanical stirrer and a drying tube and is immersed in an ice bath. A solution of 135 g. (3.0 moles) of anhydrous dimethylamine (Note 1) in 150 ml. of anhydrous benzene is introduced into the flask. The acid chloride is added very slowly from the dropping funnel to the vigorously stirred solution, the addition taking about 2 hours. The mixture is then stirred at room temperature overnight. Two hundred milliliters of water is added, the layers are separated, and the aqueous phase is extracted with two 100-ml. portions of ether. The extracts are combined with the benzene layer, washed with saturated sodium chloride solution, and dried over 100 g. of anhydrous magnesium sulfate. Most of the solvent is removed by distillation through a 20-cm. Vigreux column at atmospheric pressure, and the residual liquid is distilled through the column under reduced pressure. The fraction boiling at 85–86°/1.5 mm. is collected (Note 3). The yield of N,N-dimethylcyclohexanecarboxamide is 133–138 g. (86–89%), n_D^{25} 1.4800–1.4807.

B. *N,N-Dimethylcyclohexylmethylamine*. In a 3-l. three-necked flask equipped with a reflux condenser and a dropping funnel, both protected by drying tubes, is placed a suspension of 32 g. (0.85 mole) of lithium aluminum hydride (Note 4) in 400 ml. of anhydrous ether (Note 5). The mixture is stirred with a magnetic stirrer using a 40-mm. Teflon-covered stirring bar. A solution of 133 g. (0.85 mole) of N,N-dimethylcyclohexanecarboxamide in 300 ml. of anhydrous ether (Note 5) is added at such a rate as to maintain gentle reflux. The addition requires about 1 hour. The flask is then placed in an electric heating mantle, and the mixture is stirred and heated under reflux for 15 hours. The heating mantle is replaced by an ice bath, and the flask is fitted with an efficient mechanical, sealed stirrer. Water (70 ml.) is added slowly with vigorous stirring. Stirring is continued for 30 minutes after the addition of water is complete. A cold solu-

tion of 200 g. of sodium hydroxide in 500 ml. of water is added at once, and the flask is fitted for steam distillation. The mixture is steam-distilled until the distillate is neutral; about 1.5 l. is collected. The distillate is acidified by careful addition, with water cooling, of 95 ml. of concentrated hydrochloric acid. The two layers are separated and the ether layer washed with 50 ml. of 10% hydrochloric acid. The combined acidic solutions are concentrated until no more distillate comes over at steam bath temperature and 20 mm. pressure. The residue is dissolved in 200 ml. of water, the solution cooled, and 110 g. of sodium hydroxide pellets is added slowly, with stirring and external cooling with ice. The two layers are separated, and the aqueous phase is extracted with three 100-ml. portions of ether (Note 6). The combined amine layer and ether extracts are dried over 40 g. of potassium hydroxide pellets for 3 hours. The drying agent is separated by decantation, and the solvent is removed by distillation through a 20-cm. Vigreux column. The residue, on distillation under reduced pressure, yields 106–107 g. (88%) of N,N-dimethylcyclohexylmethylamine, b.p. 76°/29 mm., n_D^{25} 1.4462–1.4463.

2. Notes

1. The material as supplied by the Eastman Kodak Company (white label grade) may be used without further purification.

2. No fractionating column was used.

3. In some runs, small amounts of sulfur-containing compounds distilled together with the amide. These impurities did not affect the yield and purity of the N,N-dimethylcyclohexylmethylamine obtained in the subsequent reduction with lithium aluminum hydride.

4. Lithium aluminum hydride as supplied by Metal Hydrides Inc., Beverly, Massachusetts, may be used without prior pulverization.

5. Mallinckrodt absolute ethyl ether (reagent grade) may be used without further drying.

6. The checkers added enough water to dissolve most of the solid before the second and third ether extractions.

3. Methods of Preparation

N,N-Dimethylcyclohexylmethylamine has been prepared by reduction of N,N-dimethylcyclohexanecarboxamide with lithium aluminum hydride;[2,3] by the action of dimethylformamide on cyclohexanecarboxaldehyde;[4] by methylation of cyclohexylmethylamine[3,5] and of N-methylcyclohexylmethylamine by the Clarke-Eschweiler method (treatment with formaldehyde and formic acid) and by the action of dimethylamine on cyclohexylmethyl bromide.[6]

N,N-Dimethylcyclohexanecarboxamide has been prepared by the action of dimethylamine on cyclohexanecarbonyl chloride.[2,3,7]

The experimental procedure described is a modification of the method reported by Mousseron, Jacquier, Mousseron-Canet, and Zagdoun[2] and by Baumgarten, Bower, and Okamoto.[3]

[1] Massachusetts Institute of Technology, Cambridge 39, Massachusetts. Supported by the Office of Ordnance Research, U. S. Army, under Contract No. DA-19-020-ORD-4542.

[2] Mousseron, Jacquier, Mousseron-Canet, and Zagdoun, *Bull. soc. chim. France*, **1952**, 1042.

[3] Baumgarten, Bower, and Okamoto, *J. Am. Chem. Soc.*, **79**, 3145 (1957).

[4] Mousseron, Jacquier, and Zagdoun, *Bull. soc. chim. France*, **1952**, 197.

[5] Cope, Bumgardner, and Schweizer, *J. Am. Chem. Soc.*, **79**, 4729 (1957).

[6] Dunn and Stevens, *J. Chem. Soc.*, **1934**, 279.

[7] Bernhard, *Z. physiol. Chem.*, **248**, 256 (1937).

p-DITHIANE

$$\begin{matrix} CH_2SH \\ | \\ CH_2SH \end{matrix} + 2C_2H_5ONa \rightarrow \begin{matrix} CH_2SNa \\ | \\ CH_2SNa \end{matrix} + 2C_2H_5OH$$

$$\begin{matrix} CH_2SNa \\ | \\ CH_2SNa \end{matrix} + \begin{matrix} CH_2Br \\ | \\ CH_2Br \end{matrix} \rightarrow \begin{matrix} & S & \\ CH_2 & & CH_2 \\ | & & | \\ CH_2 & & CH_2 \\ & S & \end{matrix} + 2NaBr$$
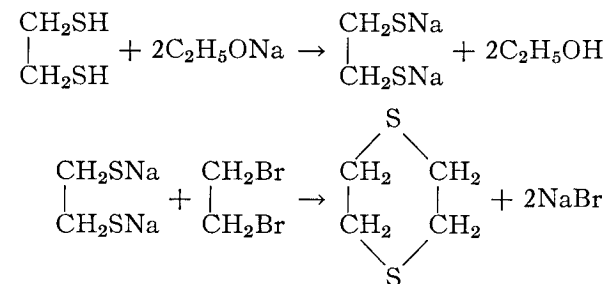
Submitted by RICHARD G. GILLIS and A. B. LACEY.[1]
Checked by B. C. McKUSICK and R. J. HARDER.

1. Procedure

In a 3-l. round-bottomed flask fitted with a mechanical stirrer and a reflux condenser is placed 2.0 l. of anhydrous ethanol. To this is added 11.5 g. (0.5 g.-atom) of sodium cut into small pieces. When the sodium is completely dissolved, 23.6 g. (21.0 ml., 0.25 mole) of 1,2-ethanedithiol[2] is added, followed by 47.0 g. (21.7 ml., 0.25 mole) of ethylene dibromide. The mixture is stirred and refluxed for 4 hours, cooled, and filtered to remove some sodium bromide mixed with polyethylene sulfide. The solid is washed with 100 ml. of ethanol, and the combined filtrates are distilled with stirring. When bumping becomes troublesome, as it generally does when 1.3–1.5 l. of distillate has been collected, the hot reaction mixture is filtered to remove sodium bromide, and the sodium bromide is washed with 100 ml. of hot ethanol.

The combined filtrates are returned to the reaction vessel, and distillation with stirring is continued until virtually all the ethanol has been removed. The distillation is stopped when crystals of *p*-dithiane appear in the condenser or when dilution of the distillate with water causes a milky appearance or the formation of a small quantity of crystals. One liter of water is added to the residue, and the stirred mixture is distilled, using the apparatus
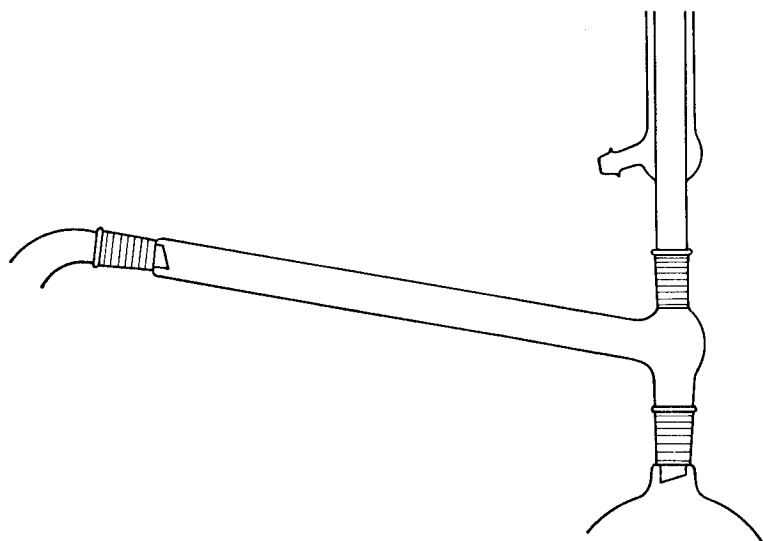
Fig. 1. Apparatus for steam distillation of a solid.

of Fig. 1 (Note 1), until no further p-dithiane solidifies in the condenser.

The dithiane is filtered and dried over phosphorus pentoxide or sodium hydroxide in a desiccator at atmospheric pressure. It melts at 112–113° and weighs 16.5–18.1 g. (55–60%).

2. Note

1. The apparatus illustrated is convenient for the steam-distillation of compounds which solidify in the condenser. By having the water condenser vertical, it can easily be cleared with a glass rod. No solidification occurs in the side arm, which behaves as a short air condenser. The adapter shown need not be specially constructed but may be assembled from commercially available components; the dimensions and joint sizes are not critical.

3. Methods of Preparation

The procedure described is essentially that of Victor Meyer.[3] p-Dithiane has also been obtained from the pyrolysis of the

polymer formed by the reaction of ethylene dibromide and potassium sulfide, either alone,[4-6] or in phenol.[7]

[1] Australian Defence Scientific Service (Defence Standards Laboratories, Department of Supply, Melbourne, Australia).
[2] Speziale, *Org. Syntheses*, **30**, 35 (1950).
[3] Meyer, *Ber.*, **19**, 3259 (1886).
[4] Crafts, *Ann.*, **124**, 110 (1862).
[5] Husemann, *Ann.*, **126**, 281 (1863).
[6] Masson, *J. Chem. Soc.*, **49**, 234 (1886).
[7] Mansfeld, *Ber.*, **19**, 697 (1886); Fuson, Lipscomb, McKusick, and Reed, *J. Org. Chem.*, **11**, 513 (1946).

ETHYL (1-PHENYLETHYLIDENE)CYANOACETATE

(Cinnamic acid, α-cyano-β-methyl-, ethyl ester)
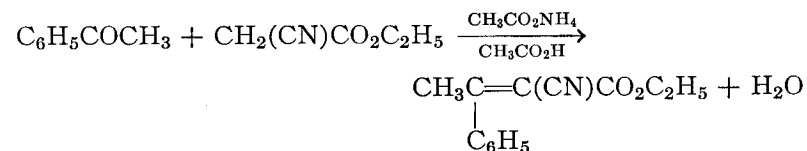
$$C_6H_5COCH_3 + CH_2(CN)CO_2C_2H_5 \xrightarrow[CH_3CO_2H]{CH_3CO_2NH_4}$$

$$CH_3C=C(CN)CO_2C_2H_5 + H_2O$$
$$\underset{C_6H_5}{|}$$

Submitted by S. M. McElvain and David H. Clemens.[1]
Checked by W. E. Parham, Perry W. Kirklin, Jr., and Wayland E. Noland.

1. Procedure

In a 1-l. three-necked round-bottomed flask fitted with a Hershberg stirrer and a constant water separator (Note 1) surmounted by a reflux condenser are placed 120 g. (1 mole) of acetophenone, 113 g. (1 mole) of ethyl cyanoacetate (Note 2), 15.4 g. (0.2 mole) of ammonium acetate, 48.0 g. (0.8 mole) of glacial acetic acid, and 200 ml. of benzene. The reaction mixture is stirred and heated under reflux for 9 hours during which time 28–33 ml. of lower layer is collected in the water separator (Note 3). To the cooled reaction mixture is added 100 ml. of benzene, and the whole is extracted with three 100-ml. portions of water. The combined aqueous layers are extracted with 30 ml. of benzene, which is then added to the organic layer from the previous

extraction. Anhydrous magnesium sulfate (15 g.) is added, and, after swirling occasionally for 10 minutes, the mixture is filtered by suction and the magnesium sulfate washed with two 25-ml. portions of benzene. The benzene is removed by distillation at reduced pressure and the residual oil distilled rapidly through a 15-cm. column. The yield of ester is 113–125 g. (52–58%), b.p. 135–160° (0.35 mm.) (Note 4).

2. Notes

1. A typical water separator has been described by Cope et al.[2]

2. Eastman Kodak white label grade acetophenone and ethyl cyanoacetate are used without further purification. The checkers used Matheson, Coleman, and Bell acetophenone and ethyl cyanoacetate without further purification.

3. The checkers used ammonium acetate which was slightly moist; consequently 33.5–34.5 ml. of lower layer was collected.

4. The checkers report the refractive index of the product to be $n_{\mathrm{D}}^{25.1}$ 1.5468–1.5469.

3. Methods of Preparation

The above procedure is essentially that described by Cope et al.[2] Ethyl (1-phenylethylidene)cyanoacetate has been prepared also by condensing acetophenone with ethyl cyanoacetate in the presence of zinc chloride and aniline.[3]

[1] Department of Chemistry, University of Wisconsin, Madison, Wisconsin.
[2] Cope, Hofmann, Wyckoff, and Hardenbergh, *J. Am. Chem. Soc.*, **63**, 3452 (1941).
[3] Scheiber and Meisel, *Ber.*, **48**, 238 (1915).

INDAZOLE

(Benzopyrazole)
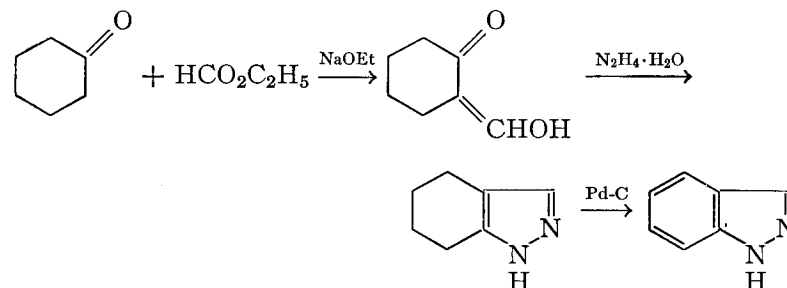
Submitted by C. Ainsworth.[1]
Checked by Max Tishler, George Gal, and G. A. Stein.

1. Procedure

A. *2-Hydroxymethylenecyclohexanone, Method 1.* A mixture of 23 g. (1 g.-atom) of sodium metal cut in approximately 1-cm. cubes, 2 l. of dry ether, 98 g. (103 ml., 1 mole) of redistilled cyclohexanone, and 110 g. (120 ml., 1.5 moles) of ethyl formate is placed in a 5-l. three-necked flask equipped with a stirrer, stopper, and vent tube. The reaction is initiated by the addition of 5 ml. of ethyl alcohol to the stirred mixture, which is then placed in a cold water bath. Stirring is continued for 6 hours. After standing overnight, 25 ml. of ethyl alcohol is added, and the mixture is stirred for an additional hour. After the addition of 200 ml. of water, the mixture is shaken in a 3-l. separatory funnel. The ether layer is washed with 50 ml. of water, and the combined aqueous extracts are washed with 100 ml. of ether. The aqueous layer is acidified with 165 ml. of 6*N* hydrochloric acid, and the mixture is extracted twice with 300 ml. of ether. The ether solution is washed with 25 ml. of saturated sodium chloride solution and then is dried by the addition of approximately 30 g. of an-

hydrous magnesium sulfate powder. The drying agent is removed by suction filtration, and the ether is evaporated on the steam bath. The residue is distilled under reduced pressure using a 6-inch Vigreux column. After a small fore-run there is obtained 88–94 g. (70–74%) of 2-hydroxymethylenecyclohexanone, b.p. 70–72°/5 mm., n_D^{25} 1.5110 (Note 1).

2-Hydroxymethylenecyclohexanone, Method 2. A mixture of 50 g. (1 mole) of 48% sodium hydride dispersed in mineral oil (Note 2), 2 l. of dry ether, and 5 ml. of ethyl alcohol is placed in a 5-l. three-necked flask equipped with a stirrer, dropping funnel, and vent tube. The reaction vessel is cooled by means of a cold water bath, and a solution of 98 g. (103 ml., 1 mole) of redistilled cyclohexanone and 110 g. (120 ml., 1.5 moles) of ethyl formate is added dropwise during 1 hour. Stirring is continued for 6 hours (Note 3), and the solution is allowed to stand overnight. After the addition of 20 ml. of ethyl alcohol, the mixture is stirred for 1 hour. Water (200 ml.) is added to the flask with stirring, the mixture is shaken in a 3-l. separatory funnel and the organic layer separated. The product is isolated according to the procedure described in Method 1. The yield of 2-hydroxymethylenecyclohexanone is the same by both methods.

B. *4,5,6,7-Tetrahydroindazole.* A solution of 63 g. (0.5 mole) of 2-hydroxymethylenecyclohexanone and 500 ml. of methyl alcohol contained in a 2-l. beaker is treated with 25 ml. (0.5 mole) of hydrazine hydrate in small portions (Note 4). After standing for 30 minutes the mixture is concentrated by warming under reduced pressure on the steam bath. To aid in removing the water, 100 ml. of ethyl alcohol is added, and again the mixture is concentrated by heating under reduced pressure. The residue is dissolved in about 100 ml. of hot petroleum ether (Note 5), and after cooling in an ice bath for 1 hour the solid that separates is collected by suction filtration and washed with a small amount of cold petroleum ether. The crude 4,5,6,7-tetrahydroindazole, m.p. 79–80°, weighs 58–60 g. (95–98%) and is sufficiently pure to be used in the next step (Notes 6 and 7).

C. *Indazole.* A mixture of 50 g. (0.41 mole) of 4,5,6,7-tetrahydroindazole, 35 g. of 5% palladium on carbon (Note 8) and 1 l. of dry Decalin is placed in a 3-l. round-bottomed flask and heated

under reflux for 24 hours. The hot mixture is filtered by suction, using a previously heated Büchner funnel, and the catalyst is washed on the funnel with 100 ml. of hot (100°) Decalin. The combined filtrate is allowed to cool and is refrigerated overnight. The indazole is collected by suction filtration and is air-dried. The product weighs 32–36 g. (66–76%) and is essentially pure indazole, m.p. 147–148° (Note 9).

2. Notes

1. 2-Hydroxymethylenecyclohexanone begins to polymerize after standing at room temperature for several days.
2. Available from Metal Hydrides Inc., Beverly, Massachusetts.
3. After an hour or so, the ether comes to a boil, and the reaction mixture is cooled in a cold water bath.
4. The reaction is exothermic but is contained in the beaker.
5. The petroleum ether fraction used was Skellysolve B (boiling range 60–70°).
6. 4,5,6,7-Tetrahydroindazole can be distilled, b.p. 135–140°/5 mm. It is recrystallized from petroleum ether and melts at 84°.
7. The petroleum ether purification step may be eliminated with equally satisfactory results. After dehydration with ethyl alcohol, the residue is dried under reduced pressure to constant weight and used directly for the next step.
8. The palladium catalyst is prepared according to *Organic Syntheses*, Coll. Vol. **3**, 686 (1955). It can be reused for the dehydrogenation of 4,5,6,7-tetrahydroindazole to indazole. The yield is somewhat better with used catalyst than with fresh catalyst.
9. Indazole is recrystallized from petroleum ether and melts at 147°.

3. Methods of Preparation

2-Hydroxymethylenecyclohexanone has been prepared by the reaction of cyclohexanone and alkyl formates.[2-4]
4,5,6,7-Tetrahydroindazole has been prepared by the hydrolysis

of 1-carbamyl-4,5,6,7-tetrahydroindazole.[2,3]   It was first pre-
pared in the Lilly Research Laboratories by Dr. N. Easton by the
reaction of 2-hydroxymethylenecyclohexanone and hydrazine
hydrate.

Indazole has been prepared according to the method reported
in *Organic Syntheses*.[5]   The present method employs milder reac-
tion conditions.   Recently, indazole has been prepared by the
hydrolysis or reduction of 3-cyanoindazole,[6] by heating 1-*o*-
tolyl-3,3-dimethyltriazine,[7] by the coupling of N-nitroso-*o*-benzo-
(or aceto)-toluidide,[8,9] and by the decomposition of *cis*-2-stil-
benediazonium fluoroborate.[10]

[1] The Lilly Research Laboratories, Indianapolis 6, Indiana.
[2] Wallach, Steindorff, and Grimmer, *Ann.*, **329**, 109 (1903).
[3] von Auwers, Buschmann, and Heidenreich, *Ann.*, **435**, 277 (1924).
[4] Plattner, Treadwell, and Scholz, *Helv. Chim. Acta*, **28**, 771 (1945).
[5] Stephenson, *Org. Syntheses*, Coll. Vol. **3**, 475 (1955).
[6] Rousseau and Lindwall, *J. Am. Chem. Soc.*, **72**, 3047 (1950).
[7] Cook, Dickson, Jack, Loudon, McKeown, MacMillan, and Williamson, *J. Chem. Soc.*, **1950**, 139.
[8] Huisgen and Nakaten, *Ann.*, **573**, 181 (1951).
[9] Huisgen and Nakaten, *Ann.*, **586**, 84 (1954).
[10] DeTar and Chu, *J. Am. Chem. Soc.*, **76**, 1686 (1954).

INDOLE-3-ALDEHYDE

(3-Indolecarboxaldehyde)
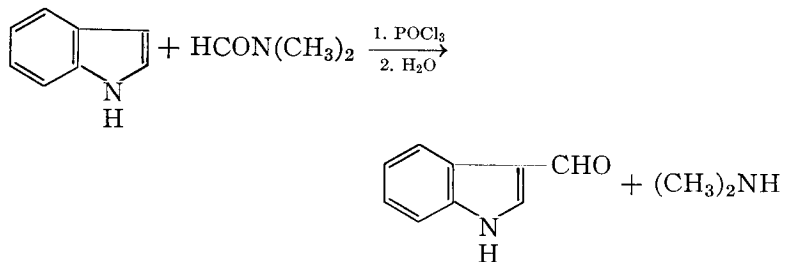
Submitted by Philip N. James and H. R. Snyder.[1]
Checked by Virgil Boekelheide and Richard N. Knowles.

1. Procedure

In a 1-l. round-bottomed, three-necked flask fitted with an
efficient mechanical stirrer, a drying tube containing Drierite,
and a 125-ml. dropping funnel is placed 288 ml. (274 g., 3.74
moles) of freshly distilled dimethylformamide (Note 1).   The
flask and its contents are cooled in an ice-salt bath for about 0.5
hour, and 86 ml. (144 g., 0.94 mole) of freshly distilled phosphorus
oxychloride (Note 2) is subsequently added with stirring to the
dimethylformamide over a period of 0.5 hour.   The pinkish color
of the formylation complex may be observed during this step.
The 125-ml. dropping funnel is replaced with a 200-ml. dropping
funnel, and a solution of 100 g. (0.85 mole) of indole (Note 3) in
100 ml. (95 g., 1.3 moles) of dimethylformamide is added to the
yellow solution over a period of 1 hour during which time the
temperature should not rise above 10°.   Once the solution is well
mixed, the dropping funnel is replaced with a thermometer, and
the temperature of the viscous solution is brought to 35°.   The
syrup is stirred efficiently at this temperature for 1 hour, or for 15
minutes longer than is necessary for the clear yellow solution to
become an opaque, canary-yellow paste (Note 4).   At the end of
the reaction period, 300 g. of crushed ice is added to the paste
(Note 5) with careful stirring, producing a clear, cherry-red
aqueous solution.

This solution is transferred with 100 ml. of water to a 3-l.
three-necked flask containing 200 g. of crushed ice and fitted
with an efficient mechanical stirrer and a separatory funnel con-
taining a solution of 375 g. (9.4 moles) of sodium hydroxide in
1 l. of water.   The aqueous base is added dropwise with stirring
until about one-third of it has been added (Note 6).   The remain-
ing two-thirds is added rapidly with efficient stirring (Note 7),
and the resulting suspension is heated rapidly to the boiling point
and allowed to cool to room temperature, after which it is placed
in a refrigerator overnight.   The precipitate is collected on a
filter and resuspended in 1 l. of water.   Most of the inorganic
material dissolves, and the product is then collected on a filter,
washed with three 300-ml. portions of water and air-dried, yield-
ing about 120 g. (97%) of indole-3-aldehyde, m.p. 196–197°.   The

indole-3-aldehyde resulting from this procedure is sufficiently pure for most purposes, but it may be recrystallized from ethanol if desired (Note 8).

2. Notes

1. Freshly distilled Merck reagent grade or du Pont technical grade, dimethylformamide, b.p. 151–153°, was used.

2. Mallinckrodt analytical reagent grade phosphorus oxychloride was freshly distilled, b.p. 106–108°.

3. Dow Chemical Company indole was employed. It was recrystallized once (150 g./1800 ml.) from 60–90° petroleum ether, m.p. 52–53°.

4. The precipitation described here did not occur in all runs, but no appreciable effect on the yield or purity of the final product was noticed if the stirring and heating of the greenish yellow solution were continued for at least one hour.

5. Reaction between the non-aqueous paste and water (or ice) is exothermic, so it is sometimes helpful to cool the paste in an ice bath before adding the ice. In any case, no trouble should be encountered provided the 300 g. of ice is added at once.

6. The point at which rapid addition should begin is easily recognized by the disappearance of the red color of the solution and the appearance of a greenish blue or greenish yellow color.

7. Near the end of the addition, the entire contents of the flask may set up solid, stopping the stirrer. The use of a powerful stirrer at this point is desirable, for by the addition of about 100 ml. of water with rapid stirring, the cake is returned to the condition of a thick slurry. During the heating period which follows, the setting-up may again occur, but rapid and efficient stirring is usually sufficient to break up the cake. By the time the temperature has reached the boiling point, a clear yellow-orange solution should be obtained.

There is considerable evolution of dimethylamine during the heating period, especially near the boiling point.

8. About 8.5 ml. of 95% ethanol is required per gram of aldehyde. The recovery of aldehyde in this recrystallization is seldom better than 85%, and the melting point is raised only 1–2°. Concentration of mother liquors to about 15% of their original volume yields another 12–13% of aldehyde which is nearly as pure as the first crop.

3. Methods of Preparation

Indole-3-aldehyde may be prepared by direct formylation of indole with dimethylformamide [2,3] or N-methylformanilide [4] using phosphorus oxychloride as a catalyst, by the Reimer-Tiemann reaction,[5,6] by a modified Gattermann reaction on 2-carbethoxyindole,[6] by formylation of the potassium salt of indole with carbon monoxide under vigorous conditions of heat and pressure,[3] by the Grignard reaction,[7] by hydrolysis and decarboxylation of the anil of 3-indolylglyoxylic acid,[8] by a modified Sommelet reaction on gramine [9] and on indole itself,[10] and by oxidation and hydrolysis of N-skatyl-N-phenylhydroxylamine.[11] The method described above is essentially that of Smith.[2] It is far superior to other methods reported for the preparation of indole-3-aldehyde because it is extremely simple and convenient, the yield of aldehyde is nearly quantitative, and the product is obtained in a state of high purity. Two other examples of the use of the dimethylformamide procedure have been described previously in *Organic Syntheses*.[12]

[1] Department of Chemistry and Chemical Engineering, University of Illinois, Urbana, Illinois.

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2-MERCAPTO-4-AMINO-5-CARBETHOXYPYRIMIDINE

(5-Pyrimidinecarboxylic acid, 4-amino-2-mercapto-, ethyl ester)

AND 2-MERCAPTO-4-HYDROXY-5-CYANOPYRIMIDINE

(5-Pyrimidinecarbonitrile, 4-hydroxy-2-mercapto-,)

$$C_2H_5OCH=C(CN)CO_2C_2H_5 + CS(NH_2)_2 \xrightarrow{C_2H_5ONa}$$
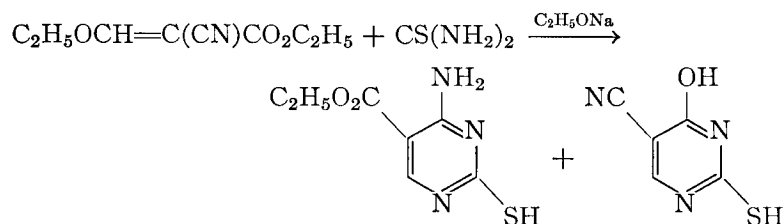
Submitted by T. L. V. ULBRICHT, TAKUO OKUDA, and CHARLES C. PRICE.[1]
Checked by B. C. McKUSICK and STEPHEN PROSKOW.

1. Procedure

A. *2-Mercapto-4-amino-5-carbethoxypyrimidine.* A 5-l. three-necked, round-bottomed flask mounted in a heating mantle is fitted with a 250-ml. dropping funnel, an efficient, sealed, mechanical stirrer, and a reflux condenser connected to a calcium chloride drying tube. Absolute ethanol (625 ml.) is placed in the flask, the stirrer is started, and 23 g. (1 g.-atom) of freshly cut sodium is added in portions. After the sodium has dissolved, 76.1 g. (1 mole) of thiourea is added to the warm, stirred solution in one portion. When the bulk of the thiourea has dissolved, 169 g. (1 mole) of liquefied ethyl ethoxymethylenecyanoacetate is added from the dropping funnel to the stirred mixture over a period of 2 hours (Note 1). This rate of addition keeps the reaction mixture warm. The solution is then stirred and gently refluxed for 6 hours. The sodium salt of the carbethoxypyrimidine may precipitate during the course of the reaction.

The reaction mixture is cooled to 50–60°, and 1.75 l. of water is added, followed by 65 ml. of acetic acid to make the mixture distinctly acidic. The resulting suspension is stirred and boiled for

5 minutes in order to effect complete decomposition of the sodium salt.

The mixture is cooled to 25°, and the crystalline 2-mercapto-4-amino-5-carbethoxypyrimidine is collected on a 10-cm. Büchner funnel and washed successively with five 50-ml. portions of water, 50 ml. of acetone, and 50 ml. of ether (Note 2). The carbethoxypyrimidine weighs 152–159 g. (76–80%) and melts with decomposition at 259–260° (Note 3) after being dried for 5 hours at 110° and atmospheric pressure. It is in the form of a cream-colored powder that is sufficiently pure for synthetic purposes. Pure carbethoxypyrimidine can be obtained by recrystallizing the crude product once from 50% acetic acid, using 170 ml. per gram of pyrimidine.

B. *2-Mercapto-4-hydroxy-5-cyanopyrimidine.* The aqueous filtrate from which the crude 2-mercapto-4-amino-5-carbethoxypyrimidine separated is cooled overnight at 0°, and the cyanopyrimidine that precipitates is collected on a suction filter. The crude product is recrystallized from about 200 ml. of 10% acetic acid with 1 g. of decolorizing charcoal added. Two additional recrystallizations done similarly give the pure cyanopyrimidine as faintly yellow crystals, m.p. 265–272° (dec.) (Note 3). The yield is 10–18 g. (7–12%).

2. Notes

1. Ethyl ethoxymethylenecyanoacetate can be prepared in the laboratory from ethyl cyanoacetate and ethyl orthoformate according to the directions of de Bellemont.[2] The submitters and checkers used a commercial product, m.p. 45–50°, obtained from Kay-Fries, Inc., New York. The liquefied product is weighed and poured into the dropping funnel. An infrared heating lamp is used to keep it liquid during the addition.

2. For complete removal of a yellow impurity, the product should be stirred well with each portion of water before filtration. If the solid is not washed with organic solvents, drying of the caked product will be slow.

3. The decomposition point is greatly dependent on the rate of heating. The checkers found that the carbethoxypyrimidine

heated on a Fisher-Johns melting-point block at a rate of 4° per minute decomposed at 280–285°. Under the same conditions, the cyanopyrimidine decomposed at 285–289°. Both products started to darken around 260°. In the infrared, the carbethoxy-pyrimidine has a strong band at 5.88 μ and no absorption in the 4.4 μ range, whereas the cyanopyrimidine has a strong band at 4.48 μ and no absorption at 5.88 μ.

3. Methods of Preparation

The described procedure is based on the methods of Johnson and Ambler [3] and Anderson et al.,[4] as modified by Ulbricht and Price.[5] This procedure is illustrative of a general method of preparing pyrimidines, wherein one condenses thiourea, guanidine, or an amidine with alkoxymethylenemalonic esters, alkoxy-methylenecyanoacetic esters, or alkoxymethylenemalononitrile. Kenner and Todd recently reviewed the synthesis of pyrimidines.[6]

2-Mercapto-4-amino-5-carbethoxypyrimidine has been converted to 2-methylmercapto-4-amino-5-hydroxymethylpyrimidine,[5] an antimetabolite possessing antitumor activity,[7] by methylation of the mercapto group followed by reduction of the ester group to a hydroxymethyl group with lithium aluminum hydride.[5]

[1] Department of Chemistry, University of Pennsylvania, Philadelphia 4, Pennsylvania, supported in part by U.S.P.H.S. Grant No. CY–2189.

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METHYL CYCLOPENTANECARBOXYLATE

(Cyclopentanecarboxylic acid, methyl ester)
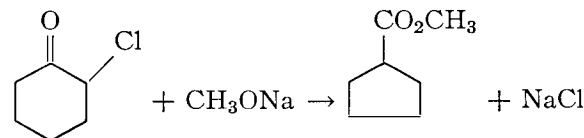
Submitted by D. W. Goheen and W. R. Vaughan.[1]
Checked by N. J. Leonard, M. J. Konz, W. H. Pittman, and K. L. Rinehart, Jr.

1. Procedure

A dry 1-l. three-necked, round-bottomed flask is equipped with an efficient stirrer (Note 1), a spiral reflux condenser, and a dropping funnel, and all openings are protected by calcium chloride drying tubes. A suspension of 58 g. (1.07 moles) of sodium methoxide (Notes 2 and 3) in 330 ml. of anhydrous ether (Note 4) is added, and stirring is begun. To the stirred suspension is added dropwise a solution of 133 g. (1 mole) of 2-chlorocyclohexanone [2] (Notes 5 and 6) diluted with 30 ml. of dry ether. The exothermic reaction is regulated by the rate of addition of the chloroketone; about 40 minutes is required for the addition. After the addition of the chloroketone is complete, the mixture is stirred and heated under reflux for 2 hours (Note 7) and is then cooled. Water is added until the salts are dissolved (Note 8). The ether layer is separated, and the aqueous layer is saturated with sodium chloride. After extraction of the aqueous layer with two 50-ml. portions of ether, the ethereal solutions are combined and washed successively with 100-ml. portions of 5% hydrochloric acid, 5% aqueous sodium bicarbonate solution, and saturated sodium chloride solution. The ether solution is dried over magnesium sulfate, and the magnesium sulfate is removed by filtration and washed with ether. Removal of the ether by distillation at atmospheric pressure leaves the crude ester, which is distilled, with fractiona-

tion (Note 9), at 70–73°/48 mm., n_D^{25} 1.4341. The yield of methyl cyclopentanecarboxylate is 72–78 g. (56–61%) (Note 10).

2. Notes

1. A mercury seal and a Hershberg stirrer made from tantalum wire are suitable.

2. Commercial (Matheson Co., Inc.) sodium methoxide is most convenient. The reaction can be run using sodium methoxide prepared from sodium and methanol, but this procedure is more tedious since it requires the removal of a considerable amount of methanol.

3. A slight excess of sodium methoxide should always be used. When an equivalent amount is employed, slightly lower yields are obtained.

4. Commercial anhydrous analytical reagent ether, from sealed cans, was employed by the checkers without further drying.

5. The 2-chlorocyclohexanone [2] employed by the checkers had b.p. 98–99°/14.5 mm., n_D^{25} 1.4826. Purity is critical in determining the yield of methyl cyclopentanecarboxylate.

6. Chlorocyclohexanone is added to the sodium methoxide, since the reverse mode of addition results in lower yields through increased formation of high-boiling condensation products.

7. The submitters report that equivalent yields are obtained when the mixture is allowed to stand overnight after the addition of the chloroketone is complete.

8. The checkers found that approximately 175 ml. of water is required.

9. The checkers employed a Podbielniak column, 0.8 x 125 cm., with tantalum wire spiral and partial reflux head.[3]

10. The residue of higher-boiling material arises from the condensation of both the starting material and the product under the influence of sodium methoxide.

3. Methods of Preparation

Methyl cyclopentanecarboxylate has been prepared by the Favorskiĭ rearrangement of 2-chlorocyclohexanone with sodium

methoxide.[4] Other alkyl esters of cyclopentanecarboxylic acid have been prepared by employing the corresponding alkoxides with 2-chlorocyclohexanone.[4-6] The Favorskiĭ reaction has been reviewed elsewhere.[7]

The methyl ester has also been obtained by esterification of cyclopentanecarboxylic acid.[8] The acid, in turn, has been prepared by the Favorskiĭ rearrangement,[6,7,9-11] by the reaction of cyclopentyl Grignard reagent with carbon dioxide,[12] by the carbonylation of cyclopentyl alcohol with nickel carbonyl[13] or with formic acid in the presence of sulfuric acid,[14] and by the hydrogenation of cyclopentene-1-carboxylic acid prepared from ethyl cyclopentanone-2-carboxylate[15] or from cyclopentanone cyanohydrin.[16]

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METHYLENECYCLOHEXANE

(Cyclohexane, methylene-)

AND N,N-DIMETHYLHYDROXYLAMINE HYDROCHLORIDE

(Hydroxylamine, N,N-dimethyl-, hydrochloride)
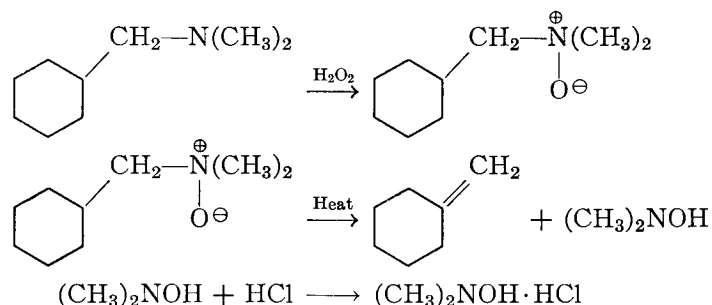
$$(CH_3)_2NOH + HCl \longrightarrow (CH_3)_2NOH \cdot HCl$$

Submitted by Arthur C. Cope and Engelbert Ciganek.[1]
Checked by William E. Parham and Robert Koncos.

1. Procedure

In a carefully cleaned 500-ml. Erlenmeyer flask, covered with a watch glass, are placed 49.4 g. (0.35 mole) of N,N-dimethylcyclohexylmethylamine (Note 1), 39.5 g. (0.35 mole) of 30% hydrogen peroxide, and 45 ml. of methanol. The homogeneous solution is allowed to stand at room temperature for 36 hours. After 2 and 5 hours hydrogen peroxide (39.5-g. portions each time) is added (Notes 2, 3). The excess hydrogen peroxide is destroyed by stirring the mixture with a small amount of platinum black (Note 4) until the evolution of oxygen ceases. The solution is filtered into a 500-ml. round-bottomed flask and concentrated at a bath temperature of 50–60° (Note 5), a water aspirator being used initially and an oil pump finally, until the amine oxide hydrate solidifies. A Teflon-covered stirring bar is introduced into the flask, which is then connected by a 20-cm. column to a trap

(reversed to avoid plugging) cooled in Dry Ice-acetone. The flask is heated in an oil bath to 90–100°, and the apparatus is evacuated to a pressure of ca. 10 mm. with stirring of the liquefied amine oxide hydrate. When the content of the flask resolidifies, the temperature of the oil bath is raised to 160°. The amine oxide decomposes completely within about 2 hours at this temperature. Water (100 ml.) is added to the contents of the trap. The olefin layer is removed with a pipette and washed with two 5-ml. portions of water, two 5-ml. portions of ice-cold 10% hydrochloric acid (Notes 6, 7), and one 5-ml. portion of 5% sodium bicarbonate solution. The olefin is cooled in a dry ice-acetone bath and filtered through glass wool (Note 8). Distillation over a small piece of sodium through a semimicro column [2] yields 26.6–29.6 g. (79–88%) of methylenecyclohexane, b.p. 100–102° (Note 9), n_D^{25} 1.4474 (Note 10).

The aqueous layer is combined with the two neutral aqueous extracts and acidified by addition of 45 ml. of concentrated hydrochloric acid. The solution is concentrated under reduced pressure at 60–70° until no more distillate comes over. The residue, which solidifies on cooling, is dried in a vacuum desiccator over potassium hydroxide pellets to yield 30.7–32.7 g. (90–96%) of crude N,N-dimethylhydroxylamine hydrochloride, m.p. 103–106° (sealed tube). Crystallization from 40 ml. of isopropyl alcohol gives 26.6–30.7 g. (78–90%) of the pure hydrochloride, m.p. 106–108° (sealed tube).

2. Notes

1. The preparation of N,N-dimethylcyclohexylmethylamine is described in *Org. Syntheses*, **39**, 19 (1959).

2. Many amines are oxidized much more rapidly than the one used in this preparation, and it is often necessary to cool such reaction mixtures in order to avoid decomposition of the amine oxide or a vigorous exothermic reaction.

3. The completion of the oxidation should be tested by adding 1 drop of an alcoholic phenolphthalein solution and 3 drops of water to 1 drop of the oxidation mixture on a porcelain spot plate. Amine oxides give no color with phenolphthalein.

4. Prepared by the procedure of Feulgen, *Ber.*, **54,** 360 (1921), and added as an aqueous suspension.

5. Some amine oxides decompose at slightly elevated temperatures. In these cases, removal of the solvents should be carried out at room temperature. It is convenient to use a rotary evaporator for removal of the solvents.

6. Methylenecyclohexane does not rearrange to 1-methylcyclohexene under these conditions. In preparations of those olefins which are more sensitive to acid, washing with acid should be omitted.

7. By making the acid extracts strongly alkaline, extracting the basic material with ether, and distilling the ether extracts, 1.0–2.5 g. (2–5%) of N,N-dimethylcyclohexylmethylamine containing a small amount of a higher-boiling basic compound of unknown structure may be recovered.

8. The material obtained in this manner is of high purity before distillation; it has the same refractive index as the distilled methylenecyclohexane, and no impurities could be detected by gas chromatographic analysis on two different columns.

9. Most of the material boils at 101–102°; the small fore-run has the same refractive index as the main fraction.

10. 1-Methylcyclohexene is completely absent, as shown by gas chromatography on a column packed with 30% by weight of a 52% solution of silver nitrate in tetraethylene glycol (Dow Chemical Company) on 48–100 mesh "firebrick" at 60°. It is estimated that the presence of less than 0.01% of this isomer could have been detected.

3. Methods of Preparation

The present preparation of methylenecyclohexane is an example of an amine oxide pyrolysis. This route from amines to olefins in many cases yields pure olefins where the alternative method, the Hofmann exhaustive methylation reaction, is accompanied by some rearrangement to more stable isomeric olefins.

Methylenecyclohexane has been prepared by treatment of cyclohexylmethyl iodide with alcoholic potassium hydroxide

solution,[3] by thermal decarboxylation of cyclohexylideneacetic acid and of cyclohexane-1-acetic acid, [4-6] and of cyclohexane-1,1-diacetic acid;[7] by pyrolysis of the xanthate,[8] the acetate,[9-12] and the stearate[13] of cyclohexanemethanol; by the action of triphenylphosphine-methylene on cyclohexanone,[14] and by the pyrolysis of N,N-dimethylcyclohexylmethylamine methohydroxide [15, 16] and of N,N-dimethylcyclohexylmethylamine N-oxide.[15, 16]

N,N-Dimethylhydroxylamine has been prepared by the action of methylmagnesium iodide on ethyl nitrate.[17]

[1] Massachusetts Institute of Technology, Cambridge 39, Massachusetts. Supported by the Office of Ordnance Research, U. S. Army, under Contract No. DA–19–020–ORD–4542.

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9-METHYLFLUORENE

(Fluorene, 9-methyl-)
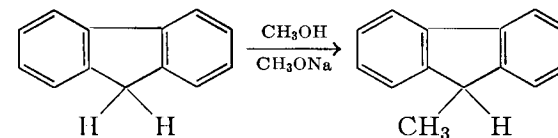
Submitted by Kurt L. Schoen and E. I. Becker.[1]
Checked by William S. Johnson and V. B. Haarstad.

1. Procedure

An 850-ml. steel bomb is charged with a solution of 23 g. (1.0 g.-atom) of sodium in 450 ml. of absolute methanol and 113 g. (0.68 mole) of fluorene (Note 1). The vessel is then closed, heated to 220° (Note 2), and rocked for 16 hours (Note 3). The reaction vessel is allowed to cool, and the contents are transferred to a 2-l. beaker with the aid of small volumes of benzene and then water to complete the transfer. The reaction mixture is diluted with an equal volume of water, neutralized with concentrated hydrochloric acid, and extracted with three 150-ml. portions of benzene. The combined benzene extracts are washed with three 200-ml. portions of water, and the solvent is removed by distillation at atmospheric pressure. The residue is recrystallized from methanol (1 l. per 100 g. of solute) to give 96–106 g. (78–86% yield) (Note 4) of colorless 9-methylfluorene, m.p. 44–45° (Note 5).

2. Notes

1. A commercial grade of fluorene was purified by crystallization from methanol until the m.p. was 113–114°.

2. In the checkers' experience the temperature must not be below 220° or a diminution in yield will result.

3. Without rocking, the crude product is colored and the yield is slightly lower.

4. This is a total yield of material obtained in 2–3 crops. In a typical run the first crop amounted to 90 g., m.p. 44–45°, and the second, obtained on concentrating and cooling the mother liquor, amounted to 16 g., m.p. 44–45°.

The crude product may alternatively be purified by rapid distillation at reduced pressure to give 114–116 g., b.p. 95–100°/1 mm. Redistillation affords 102–105 g. (81–84% yield), b.p. 96–98°/0.6 mm., of colorless 9-methylfluorene which solidifies.

5. The submitters state that the procedure is general and has been carried out with normal alcohols from C_1 to C_7. In an analogous procedure 10 g. of fluorene was treated with 40 ml. of alcohol and 2.3 g. of sodium (in a Carius tube) to give 52–84%

of redistilled 9-alkylfluorene. 9-n-Octadecylfluorene was prepared from 13.3 g. of fluorene, 16.2 g. of n-octadecyl alcohol, and 2 g. of sodium. In this case the reaction was carried out in a flask (equipped with a condenser) that was heated in an oil bath for 16 hours at 210°. The solid product was purified by crystallization.

Product	B.P./1 mm.	n_D^{25}	d_4^{25}	Yield, %
9-Ethylfluorene	123–124°	1.6180	1.0508	84
9-n-Propylfluorene	126–128°	1.6050	1.0326	72
9-n-Butylfluorene	140°	1.5956	1.0197	78
9-n-Pentylfluorene	144–146°	1.5929	1.0153	66
9-n-Hexylfluorene	156–158°	1.5757	0.9900	68
9-n-Heptylfluorene	163–165°	1.5717	0.9827	58
9-n-Octadecylfluorene	65–66.4° (m.p.)	—	—	92

3. Methods of Preparation

Generally, fluorene has been alkylated in the 9-position by reaction of 9-acyl- or ester-substituted fluorenes with sodium alkoxide and an alkyl halide followed by removal of the activating group, by treating a 9-fluorenyl organometallic compound with an alkyl halide, by reduction of a 9-fluorenylidene derivative, by hydrogenolysis of a 9-alkyl-9-hydroxyfluorene, by hydrogenolysis of a 9-halogen-9-alkylfluorene, and by cyclization of a diphenylalkyl carbinol with phosphorus pentoxide.[2] The present procedure is based on the method of Shoen and Becker.[3]

9-Methylfluorene has been prepared by cleavage of ethyl 9-methyl-9-fluorenylglyoxylate,[4] by the decarboxylation of 9-methylfluorene-9-carboxylic acid,[4] by the decarboxylation of 9-fluorenylacetic acid,[5] by the cleavage of 9-methyl-9-acetylfluorene with alcoholic potassium hydroxide or soda-lime,[6] by the reduction of 9-methyl-9-fluorenol with hydriodic acid in acetic acid,[7] by the reaction of 9-fluorenyllithium[8] or -sodium[9] with methyl iodide or methyl sulfate,[9] by the cyclization of diphenylmethyl carbinol over platinum-on-carbon at 300°,[10] by the reaction of ethyl 9-methoxymethyl-9-fluorenylcarboxylate,[11] by the diazotization and heating of 2-ethyl-2-aminobiphenyl,[12] by the dehydration and then reduction of 9-methyl-9-fluorenol,[13]

by the thermal decomposition of tetramethylammonium 9-fluo-renide,[14] and by recovery from coal tar.[15]

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

[2] Josephy and Radt, *Elsevier's Encyclopedia of Organic Chemistry*, Vol. 13, Series III, pp. 29 ff., Elsevier Publishing Company, Inc., New York, 1946.

[3] Shoen and Becker, *J. Am. Chem. Soc.*, **77**, 6030 (1955).

[4] Wislicenus and Mocker, *Ber.*, **46**, 2772 (1913).

[5] Mayer, *Ber.*, **46**, 2579 (1913).

[6] Meerwein, *Ann.*, **396**, 242 (1913).

[7] Wanscheidt and Moldavski, *Ber.*, **64**, 917 (1931).

[8] Blum-Bergmann, *Ann.*, **484**, 26 (1930).

[9] Greenhow, White, and McNeil, *J. Chem. Soc.*, **1951**, 2848.

[10] Zelinsky and Gawerdowskaja, *Ber.*, **61**, 1049 (1928).

[11] Pinck and Hilbert, *J. Am. Chem. Soc.*, **69**, 723 (1947).

[12] Mascarelli and Longo, *Gazz. chim. ital.*, **71**, 397 (1941).

[13] Badger, *J. Chem. Soc.*, **1941**, 535.

[14] Wittig, Heintzeler, and Wetterling, *Ann.*, **557**, 201 (1947).

[15] I. G. Farbenind, A.-G. (Pier and Schoenemann), Ger. pat. 659,878 (May 12, 1938) [*C.A.*, **32**, 6844 (1938)].

3-METHYL-2-FUROIC ACID

(2-Furoic acid, 3-methyl-)

AND 3-METHYLFURAN

(Furan, 3-methyl-)
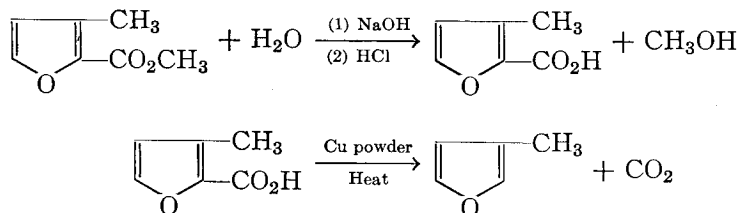
Submitted by D. M. Burness.[1]
Checked by James Cason and Robert B. Hutchison.

1. Procedure

A. *3-Methyl-2-furoic acid.* A mixture of 35 g. (0.25 mole) of methyl 3-methyl-2-furoate[2] and 80 ml. of aqueous 20% sodium

hydroxide is heated under reflux for 2 hours. The solution is cooled, acidified with about 50 ml. of concentrated hydrochloric acid (sp. gr. 1.18), stirred vigorously for a few minutes to ensure freeing of the acid from its salt, then cooled to room temperature before the product is collected by suction filtration. The product is washed with about 25 ml. of water used in two portions, drained well on the funnel, then dried. The yield of essentially pure 3-methyl-2-furoic acid is 28.5–29.5 g. (90–93%), m.p. 134–135° (Note 1).

B. *3-Methylfuran.* A mixture of 25 g. of 3-methyl-2-furoic acid, 50 g. of quinoline (Note 2), and 4.5 g. of copper powder is placed in a 125-ml. round-bottomed flask attached by a ground joint to a 30-cm. simple Vigreux column which delivers to a water-cooled condenser. The condenser is connected to a small distilling flask which serves as a receiver, with the tip of the condenser extending to the edge of the bulb of the flask. The receiver is cooled in an ice-salt bath (Note 3). The round-bottomed flask is heated by means of an electric mantle or liquid bath.

When the quinoline is heated to boiling by raising the bath temperature to about 250°, carbon dioxide is evolved at a moderate rate; the reaction is usually completed in 2–3 hours. Near the end of the reaction, heat is increased to about 265°, and the last distillate is collected until the temperature at the top of the column begins to rise rapidly above 65°. The contents of the receiver are decanted from any ice present and dried over about 1.5 g. of anhydrous magnesium sulfate, followed by Drierite, in a tightly closed flask. Redistillation yields 13.5–14.5 g. (82–88%) of colorless 3-methylfuran, b.p. 65.5–66°, n_D^{25} 1.4295–1.4315 (Notes 4 and 5).

2. Notes

1. In a run thirty times the size described, the submitters obtained a yield of 85%.

2. The quinoline should be dried by distillation from anhydrous barium oxide.

3. For larger runs, the side arm of the distilling flask should be attached to a cold trap immersed in an ice-salt bath, for about 10% of the product is likely to pass through the first receiver.

4. The product turns yellow on standing, even overnight. It can be stabilized with 0.1% hydroquinone or similar material.[3]

5. The submitter obtained similar results in runs about twenty times the size described. Over-all yields for the four steps starting with 4,4-dimethoxy-2-butanone [2] were consistently in the range 50–55%.

3. Methods of Preparation

3-Methyl-2-furoic acid has been prepared by the oxidation of 3-methyl-2-furaldehyde [4] and by the degradation of 3-methyl-2-isovalerylfuran (Elsholtzia ketone).[5] 3-Methylfuran has been prepared by the present method [6] and more recently by a three-step method starting with methallyl chloride and ethyl orthoformate.[7] Circuitous routes from citric acid [8] and malic acid [9] have also been used.

[1] Eastman Kodak Co., Rochester, New York.

[2] Burness, *Org. Syntheses*, **39**, 49 (1959).

[3] Cass, U. S. pat. 2,489,265 (1949, to du Pont) [*C.A.*, **44**, 1543 (1950)].

[4] Reichstein, Zschokke and Goerg, *Helv. Chim. Acta*, **14**, 1277 (1931).

[5] Asahina and Murayama, *Arch. Pharm.*, **252**, 442 (1914); Asahina, *Acta phytochim. (Japan)*, **2**, 12 (1924) [*Chem. Zentr.*, **1924**, II, 1694].

[6] Burness, *J. Org. Chem.*, **21**, 102 (1956).

[7] Cornforth, *J. Chem. Soc.*, **1958**, 1310.

[8] Rinkes, *Rec. trav. chim.*, **50**, 1127 (1931); Reichstein and Zschokke, *Helv. Chim. Acta*, **14**, 1270 (1931).

[9] Gilman and Burtner, *J. Am. Chem. Soc.*, **55**, 2903 (1933).

METHYL 3-METHYL-2-FUROATE

(2-Furoic acid, 3-methyl-, methyl ester)

$$(CH_3O)_2CHCH_2COCH_3 + ClCH_2CO_2CH_3 \xrightarrow{NaOCH_3}$$

$$(CH_3O)_2CHCH_2\overset{CH_3}{\underset{O}{C}}\!\!-\!\!CHCO_2CH_3 + NaCl$$

$$(CH_3O)_2CHCH_2\overset{CH_3}{\underset{O}{C}}\!\!-\!\!CHCO_2CH_3 \xrightarrow{160°}$$

$$\overset{CH_3}{\underset{CO_2CH_3}{}} + 2CH_3OH$$
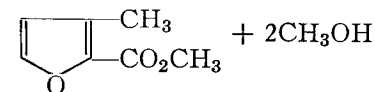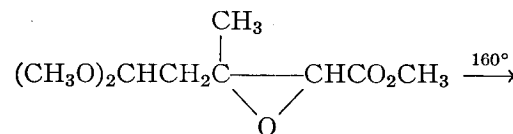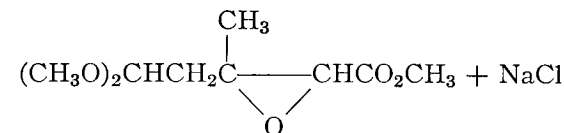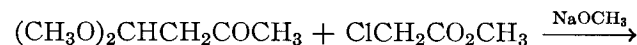
Submitted by D. M. BURNESS.[1]

Checked by JAMES CASON and ROBERT B. HUTCHISON.

1. Procedure

A. *Methyl 5,5-dimethoxy-3-methyl-2,3-epoxypentanoate.* A 2-l. three-necked flask is equipped with a sealed centrifugal stirrer (Note 1), a thermometer inserted through an adapter with a side arm connected to a source of dry nitrogen, and a 250-ml. Erlenmeyer addition flask.[2] The apparatus is dried with a free flame in a slow stream of nitrogen; from this point the reaction is conducted in an atmosphere of nitrogen (Note 2).

A mixture of 132 g. (1.0 mole) of 4,4-dimethoxy-2-butanone (Note 3), 174 g. (1.6 moles) of methyl chloroacetate (Note 3), and 800 ml. of dry ether is placed in the reaction flask, then 86 g. (1.6 moles) of sodium methoxide (Note 4) is placed in the addition flask. The solution is cooled in an ice-salt bath to −10°, then the sodium methoxide is added gradually at a rate such that a temperature below −5° can be maintained (about 2 hours).

The mixture is stirred for an additional 2 hours (Note 5) and then allowed to come to room temperature overnight. It is cooled again to 0° and made slightly acidic by the addition of a solution of 10 ml. of glacial acetic acid in 150 ml. of water. The ether is decanted, and the residual slurry is extracted with three 100-ml. portions of ether. The combined ether solutions are washed in a separatory funnel with 50 ml. of saturated sodium chloride solution to which is added 1-g. portions of sodium bicarbonate until the washings are no longer acidic. After each bicarbonate addition, the mixture is shaken for at least 1 minute before a test for acidity is made. Finally, the ether phase is washed with saturated sodium chloride solution, then dried over 20–25 g. of anhydrous magnesium sulfate. Distillation of the solvent leaves a nearly quantitative yield of crude glycidic ester (Note 6).

B. *Methyl 3-methyl-2-furoate.* The crude glycidic ester prepared as described above is placed in a 300-ml. flask which is attached to a 12-cm. column filled with $3/_{16}$-inch glass helices (or a 50-cm. simple Vigreux column) and heated in a liquid bath. When the pot temperature reaches about 160°, or before, methanol begins to distil. Heating is continued until the distillation of methanol essentially ceases and about the theoretical amount (64 g.) has been collected. After the heating bath has been allowed to cool, the product is distilled at reduced pressure; b.p. 72–78°/8 mm., yield 91–98 g. (65–70%) (Note 7). The ester solidifies in the receiver as an essentially pure compound, m.p. 34.5–36.5° (Note 8).

2. Notes

1. A stirring assembly which makes use of a lubricated ball-joint seal [3] is convenient. The checkers used a Hershberg stirrer rather than a centrifugal stirrer.

2. Maintenance of a low positive pressure of nitrogen on the system is accomplished by insertion of a T-tube in the nitrogen line for attachment of a U-tube whose bend is just closed with mineral oil.

3. The 4,4-dimethoxy-2-butanone [4] may be obtained from Aldrich Chemical Co., Milwaukee, Wisconsin, under the name of 3-ketobutyraldehyde dimethyl acetal. This and the methyl

chloroacetate are preferably dried over Drierite and distilled before use. The pure acetal has b.p. 55–56°/8 mm., n_D^{25} 1.4119. The presence of 4-methoxy-3-buten-2-one, which raises the index of refraction, can be tolerated as an impurity, for it leads to the same reaction product.[5] Commercial methyl chloroacetate usually contains considerable low-boiling material which is best separated by distillation through a 50-cm. simple Vigreux column. The chloroacetate is collected at 131–132°.

4. The submitter reports that the commercial 95% "Sodium Methylate" from Mathieson Chemical Corp. is satisfactory, provided that either fresh material or material which has been opened previously only under dry nitrogen is used. The checkers experienced such erratic results with commercial sodium methoxide (even previously unopened bottles) that freshly prepared material was used. For this purpose, 37 g. of clean sodium, cut in 1- to 3-g. pieces, was added portionwise to 800 ml. of stirred anhydrous methanol contained in a 2-l. three-necked flask equipped with a condenser. After the sodium had dissolved, the methanol was removed by distillation at reduced pressure, and the residual white sodium methoxide was dried by heating at 150° under aspirator vacuum.

5. The stream of nitrogen may be discontinued at this point if the outlet tube from the flask is closed with a Drierite tube.

6. The submitter reports that the residual glycidic ester was distilled through a 15-cm. Vigreux column to yield 185–195 g. of crude product, b.p. 113–122°/8 mm. Redistillation through a 25-cm. column packed with $3/_{16}$-inch glass helices was reported to give 157–164 g. (77–80%) of product; b.p. 93°/0.7 mm. to 89°/1 mm.; n_D^{25} 1.4405–1.4419. The drop in boiling point was attributed to decomposition during distillation to yield methanol and methyl 3-methyl-2-furoate. The checkers found that in most runs the product obtained from the first distillation consisted largely of the furoate.

The submitter has prepared methyl 5,5-dimethoxy-3-phenyl-2,3-epoxypentanoate by essentially the same procedure as here described.

7. In a run 15 times this size, a 71% yield was obtained by the submitter.

8. Recrystallization from ethanol raises the melting point to 36.5–37°.

3. Methods of Preparation

Methyl 5,5-dimethoxy-3-methyl-2,3-epoxypentanoate has been prepared only by the procedure described or in like manner from 4-methoxy-3-buten-2-one.[5]

Methyl 3-methyl-2-furoate has been prepared previously, presumably from the acid.[6]

[1] Eastman Kodak Co., Rochester, New York.
[2] Leffler and Calkins, *Org. Syntheses*, Coll. Vol. **3**, 550 (1955).
[3] *Organic Chemical Bulletin*, **24**, No. 3, Eastman Kodak Co., Rochester, N. Y., 1952.
[4] Burness, U. S. pat. 2,760,985 (August 28, 1956) [*C.A.*, **51**, 2854 (1957)].
[5] Burness, *J. Org. Chem.*, **21**, 102 (1956).
[6] Asahina, *Acta phytochim.* (*Japan*), **2**, 12 (1924) [*Chem. Zentr.*, **1924**, II, 1694].

β-METHYL-β-PHENYL-α,α'-DICYANOGLUTARIMIDE

(Glutarimide, 2,4-dicyano-3-methyl-3-phenyl-)
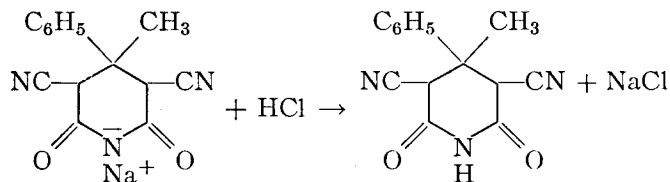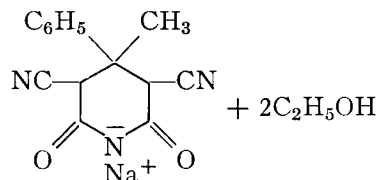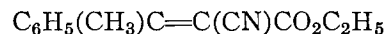
$C_6H_5(CH_3)C=C(CN)CO_2C_2H_5$

$+ CH_2(CN)CONH_2 + NaOC_2H_5 \rightarrow$

Submitted by S. M. McElvain and David H. Clemens.[1]
Checked by W. E. Parham, Perry W. Kirklin, Jr.,
and Wayland E. Noland.

1. Procedure

In a 2-l. Erlenmeyer flask fitted with a reflux condenser and arranged for magnetic stirring are placed 400 ml. of absolute ethanol (Note 1) and 11.5 g. (0.5 g.-atom) of sodium added in small portions. After the sodium has reacted (Note 2), the clear solution is cooled to room temperature, and 42.0 g. (0.5 mole) of finely powdered cyanoacetamide (Note 3) is added with stirring over a period of 1 minute. Immediately thereafter 107.6 g. (0.5 mole) of ethyl (1-phenylethylidene) cyanoacetate [2] is added. After about 20 minutes, the mixture becomes homogeneous and is allowed to stand at room temperature for 2 hours. Water (650 ml.) is added, followed by 100 ml. of concentrated hydrochloric acid in 1 portion. The resulting suspension is stirred thoroughly with a glass rod and placed in a refrigerator overnight. The product is then filtered by suction. The filter cake is sucked as dry as possible using a rubber dam, stirred to a paste with a mixture of 150 ml. of water and 50 ml. of 95% ethanol, and sucked dry. This process is repeated using 200 ml. of water, and the product is dried to constant weight in an oven at 45°. The yield is 114–116 g. (90–92%) of the dicyanoglutarimide, m.p. 274–278° (dec.) (Note 4).

2. Notes

1. Commercially available absolute ethanol is used without further drying.

2. The checkers report that the sodium ethoxide solution should be used promptly in order to avoid the formation of colored impurities.

3. Eastman Kodak white label grade is used after grinding in a mortar.

4. Recrystallization from absolute ethanol gives glistening plates melting at 286–287° (dec.).

3. Methods of Preparation

β-Methyl-β-phenyl-α,α′-dicyanoglutarimide has been prepared in low yield by the Guareschi condensation of acetophenone, ethyl cyanoacetate, and ammonia.[3]

[1] Department of Chemistry, University of Wisconsin, Madison, Wisconsin.

[2] McElvain and Clemens, *Org. Syntheses*, **39**, 25 (1959).

[3] Phalnikar and Nargund, *J. Univ. Bombay*, **6**, Pt. II, 102 (1937) [*C.A.*, **32**, 3763 (1938)].

β-METHYL-β-PHENYLGLUTARIC ACID

(Glutaric acid, 3-methyl-3-phenyl-)
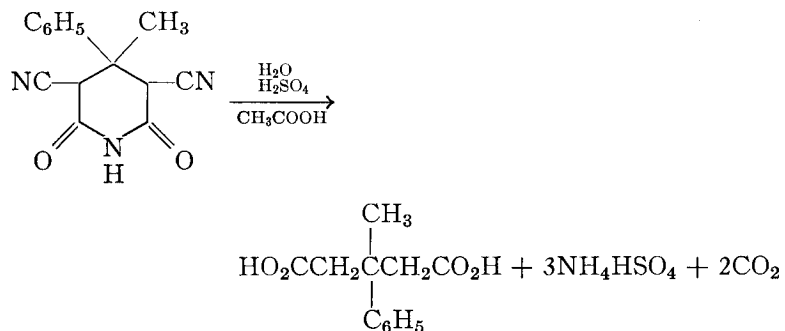
$$HO_2CCH_2\overset{\overset{\displaystyle CH_3}{|}}{C}CH_2CO_2H + 3NH_4HSO_4 + 2CO_2$$

Submitted by S. M. McElvain and David H. Clemens.[1]
Checked by W. E. Parham, Perry W. Kirklin, Jr., and Wayland E. Noland.

1. Procedure

In a 3-l. round-bottomed flask fitted with a small glass paddle stirrer and a reflux condenser are placed 101 g. (0.4 mole) of β-methyl-β-phenyl-α,α′-dicyanoglutarimide,[2] and a mixture of 500 ml. of water, 500 g. of concentrated sulfuric acid, and 400 ml. of glacial acetic acid. Without starting the stirrer (Note 1), the mixture is heated under reflux for 2 hours. Then the stirrer is cautiously started, and reflux is continued for a total of 80 hours. The reaction mixture is transferred to a 6-l. Erlenmeyer flask, 3 l.

of water is added and the mixture cooled in a refrigerator overnight. The precipitated acid is filtered by suction (Note 2), washed with 100 ml. of water, and air-dried to constant weight. The crude, dry product is swirled for 5 minutes with 200 ml. of benzene, filtered by suction, washed with two 100-ml. portions of benzene, and again air-dried. The yield of acid, m.p. 136–140°, is 64.5–68 g. (72.5–76.5%) (Notes 3 and 4).

2. Notes

1. Use of the stirrer during the first 2 hours of the hydrolysis results in excessive foaming.

2. In some runs a small amount of dark tar adhered to the side of the flask. This material was not isolated in the filtration.

3. The product is pure enough for most purposes, but it may be further purified by recrystallization from water (100 ml. for 20 g. of acid) to give material melting at 140–142° in 95% yield.

4. If the alkyl group of a β-alkyl-β-phenyl-α,α′-dicyanoglutarimide is larger than the methyl group, the hydrolysis to the corresponding glutaric acid should be modified as described by McElvain and Clemens, *J. Am. Chem. Soc.*, **80**, 3915 (1958).

3. Methods of Preparation

β-Methyl-β-phenylglutaric acid has been prepared by the hydrolysis of β-methyl-β-phenyl-α,α′-dicyanoglutarimide with sulfuric acid, and also by acid hydrolysis of the condensation product of 1,1-dichloroethylbenzene and ethyl sodiomalonate.[3]

[1] Department of Chemistry, University of Wisconsin, Madison, Wisconsin.

[2] McElvain and Clemens, *Org. Syntheses*, **39**, 52 (1959).

[3] Phalnikar and Nargund, *J. Univ. Bombay*, **6**, Pt. II, 102 (1937) [*C.A.*, **32**, 3763 (1938).

1-PHENYL-1-PENTEN-4-YN-3-OL

(1-Penten-4-yn-3-ol, 1-phenyl-)

$$HC{\equiv}CH + C_2H_5MgBr \xrightarrow{\text{Tetrahydrofuran}} HC{\equiv}CMgBr + C_2H_6$$

$$HC{\equiv}CMgBr + C_6H_5CH{=}CHCHO \xrightarrow[NH_4Cl]{H_2O}$$

$$HC{\equiv}CCHOHCH{=}CHC_6H_5$$
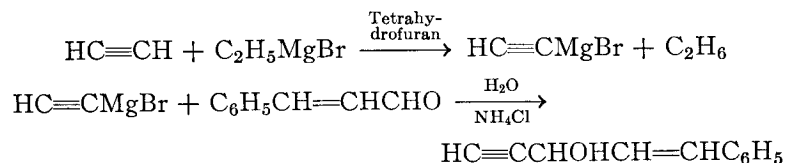
Submitted by Lars Skattebøl, E. R. H. Jones, and Mark C. Whiting.[1]
Checked by Melvin S. Newman and Raymond E. Dessy.

1. Procedure

A. *Ethynylmagnesium bromide.* A 500-ml. three-necked flask, equipped with a sealed mechanical stirrer, a reflux condenser, and a pressure-equalized dropping funnel, is arranged for carrying out a reaction in an atmosphere of nitrogen by fitting into the top of the condenser a T-tube attached to a low-pressure supply of nitrogen and to a mercury bubbler. For later use there is also prepared a dry 1-l. three-necked flask equipped with a sealed mechanical stirrer, a gas inlet tube which will dip below the surface of 200 ml. of liquid in the flask, a 500-ml. dropping funnel, and a gas outlet protected by a calcium chloride drying tube.

The 500-ml. flask is dried by warming with a soft flame as a slow stream of nitrogen is passed through the system. A solution of ethylmagnesium bromide is prepared in this flask from 12 g. (0.5 g.-atom) of magnesium turnings, 60 g. (0.55 mole) of ethyl bromide (dried over calcium chloride), and 300 ml. of tetrahydrofuran (Notes 1 and 2).

After the preparation of ethylmagnesium bromide is completed, the separatory funnel is replaced by a bent tube which reaches the bottom of the flask and is bent at the outer end for downward delivery (Note 3). The warm (40–50°) solution is forced under nitrogen pressure (by carefully pinching off the tube to the mercury bubbler) into the 500-ml. separatory funnel which has been prepared for attachment to the 1-l. flask. After all the solution has passed into the separatory funnel, nitrogen flow is allowed to continue briefly in order to displace the air above the solution, then the funnel is stoppered loosely and attached to the 1-l. flask. Two hundred milliliters of purified tetrahydrofuran is now placed in the flask, acetylene (Note 4) is introduced through the gas-inlet tube at the rate of 15–20 l. per hour, and the stirrer is started. After 5 minutes, about 5 ml. of the solution of ethylmagnesium bromide is added in 1 portion. Almost at once, there appears a froth of ethane which is easily distinguishable from the larger bubbles of acetylene. When the frothing subsides, portionwise addition of the ethylmagnesium bromide solution is continued until the total solution has been added. This requires about 3 hours, and the temperature of the reaction rises 5–10° above room temperature. The solution of ethynylmagnesium bromide is homogeneous at 30° (Note 5).

B. *1-Phenyl-1-penten-4-yn-3-ol.* The stirred solution of ethynylmagnesium bromide is cooled in ice water as there is added dropwise during about 45 minutes a solution of 47.5 g. (0.37 mole) of freshly distilled cinnamaldehyde (Note 6) in 50 ml. of purified tetrahydrofuran. After addition is complete, stirring is continued overnight as the solution is allowed to warm to room temperature. The brown homogeneous reaction mixture is added carefully to 1.5 l. of cooled saturated ammonium chloride solution, then the aqueous phase is extracted with three 250-ml. portions of ether. The ether extracts are combined with the tetrahydrofuran solution and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the product is distilled (Note 7) at a pressure of about 0.1 mm., with the heating bath at about 90°. The distillate, which solidifies on cooling, is crystallized from petroleum ether (b.p. 40–60°) to yield 33–39 g. (55–65%) of the unsaturated alcohol of m.p. 67–68° (Note 8).

2. Notes

1. If less solvent is used, the ethylmagnesium bromide may crystallize on cooling.

2. If ether is substituted for tetrahydrofuran in this preparation, the acetylenic glycol is the sole product. The submitters

purified the tetrahydrofuran by shaking with potassium hydroxide pellets, heating under reflux with sodium metal, and finally distilling. They report that heating under reflux with sodium diphenylketyl gives a better sample of tetrahydrofuran, but that this does not improve the yield.

The checkers purified the solvent by shaking with potassium hydroxide, distilling from lithium aluminum hydride, then storing over sodium wire.

3. It is advisable to prepare the delivery tube prior to its need.

4. The submitters purified the acetylene by passing it through a trap cooled to −80°, then through concentrated sulfuric acid, and finally through soda-lime. The checkers purified the acetylene by passing it first through a tower of 10-mesh alumina, then through concentrated sulfuric acid.

5. No outside cooling is employed during the preparation of ethynylmagnesium bromide. If this solution of ethynylmagnesium bromide is cooled to 0°, a crystalline complex separates. If part of the solvent is evaporated, even at 40° under reduced pressure, there occurs disproportionation to acetylene and the bisbromomagnesium derivative.

6. Methyl ethyl ketone, crotonaldehyde, and acrolein react similarly with ethynylmagnesium bromide. The respective yields of acetylenic alcohols are 69%, 84%, and 40%.

7. The submitters used a still of the evaporative type, such as a Hickman still. The checkers used a similar still modified to include a magnetic stirring bar. This modification greatly decreases the time required for removal of the last traces of solvent, minimizes the danger of bumping just before evaporative distillation occurs, and increases the rate of distillation of the product.

8. The checkers report yields as high as 84% and believe that the use of magnetic stirring in the Hickman still is responsible for the higher yield.

3. Methods of Preparation

The preparation of ethynylmagnesium bromide in ether has been described;[2,3] however, the subsequent history of the compound has been controversial. The submitters have been unable to prepare ethynyl carbinols by the earlier procedures.

1-Phenyl-1-penten-4-yn-3-ol has been prepared in liquid ammonia from cinnamaldehyde and sodium acetylide in 2% yield,[4] and from the sodium bisulfite compound of cinnamaldehyde and sodium acetylide in 13.5% yield.[5] The present procedure is based on a recent publication.[6]

[1] The Dyson Perrins Laboratory, Oxford, England.
[2] Salkind and Rosenfeld, Ber., 57, 1690 (1924).
[3] Grignard, Lapayre, and Tcheou, Compt. rend., 187, 517 (1928).
[4] Jones and McCombie, J. Chem. Soc., 1942, 733.
[5] Cymerman and Wilks, J. Chem. Soc., 1950, 1208.
[6] Jones, Skattebøl, and Whiting, J. Chem. Soc., 1956, 4765.

PHENYLPROPARGYL ALDEHYDE DIETHYL ACETAL

(Propiolaldehyde, phenyl-, diethyl acetal)

$$C_6H_5C{\equiv}CH + HC(OC_2H_5)_3 \xrightarrow[\Delta]{ZnI_2}$$
$$C_6H_5C{\equiv}C{-}CH(OC_2H_5)_2 + C_2H_5OH$$
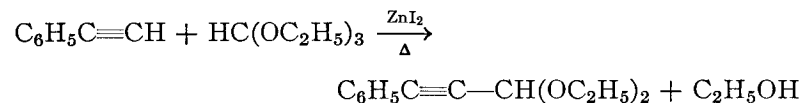
Submitted by B. W. Howk and J. C. Sauer.[1]
Checked by N. J. Leonard and S. W. Blum.

1. Procedure

Into a 300-ml. three-necked flask equipped with a nitrogen inlet, a thermometer, and a short fractionating column (Note 1) are charged 74.1 g. (0.50 mole) of triethyl orthoformate, 51.0 g. (0.50 mole) of phenylacetylene (Note 2), and 3.0 g. of zinc iodide (Note 3). Ethanol is slowly distilled from the reaction mixture, which must be heated to about 135° before refluxing in the stillhead begins. A total of 29–35 ml. of distillate, b.p. 65–88° (mostly 78°), is collected over a period of about 1 hour as the temperature of the reaction mixture gradually rises to 200° to 210° (Note 4). The reaction mixture is cooled to room temperature and filtered with suction. The flask and the small amount of precipitate on the filter paper are washed with 5 ml. of ether. The filtrate and ether washings are combined and distilled. After

a small fore-run, phenylpropargyl aldehyde diethyl acetal is collected at 99–100°/2 mm. The yield is 73–80 g. (72–78%), n_D^{25} 1.5153–1.5158. The synthesis is applicable to the preparation of other propargyl aldehyde acetals (Note 5).

2. Notes

1. The checkers found a 12-inch Vigreux column satisfactory.

2. The checkers purchased pure phenylacetylene from Gesellschaft für Teerverwertung mbH., Duisburg-Meiderich, Germany.

3. The submitters report that zinc nitrate appears to be equivalent to zinc iodide as a catalyst and that zinc chloride (commercial anhydrous grade) is satisfactory but requires 2–3 hours of heating and gives 64–70% yield.

4. Yields are lower under forcing conditions of prolonged heating.

5. The method has been applied by the submitters[2] to the preparation of cyclohexylmethylpropiolaldehyde diethyl acetal (54% yield) from cyclohexylmethylacetylene and triethyl orthoformate; of phenylethynyl n-butyl dimethyl ketal (40% yield) from phenylacetylene and trimethyl n-orthovalerate; and of phenylethynyl methyl diethyl ketal (34% yield) from phenylacetylene and triethyl orthoacetate. n-Butylpropiolaldehyde diethyl acetal was isolated in 32% yield by heating an equimolar mixture of 1-hexyne and triethyl orthoformate containing catalytic amounts of a zinc chloride-zinc iodide catalyst under autogenous pressure at 190° for 3 hours.

3. Methods of Preparation

The described method of preparing phenylpropargyl aldehyde diethyl acetal is that of Howk and Sauer.[2] The method for synthesizing phenylpropargyl aldehyde diethyl acetal previously published in *Organic Syntheses*[3] involves three steps beginning with cinnamaldehyde; over-all yields are 49–62%. Other methods of preparative value are the interaction of the Grignard reagent of phenylacetylene with triethyl orthoformate, or the

sodium derivative of phenylacetylene with either triethyl orthoformate or ethyl formate. These reactions are discussed critically by Raphael.[4] Phenylpropargyl aldehyde diethyl acetal has also been made by the action of the phenyl Grignard reagent with the diethyl acetal of chloropropiolaldehyde.[5]

The acetylenic acetals are easily hydrolyzed to the corresponding aldehydes in high yields in the presence of dilute acids.[3,4] Acetylenic acetals have also been of value in the synthesis of α,β-unsaturated ethylenic acetals or aldehydes by partial catalytic hydrogenation of the triple bond.[4]

[1] Contribution No. 474 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours & Co. (Inc.), Wilmington, Delaware.

[2] Howk and Sauer, *J. Am. Chem. Soc.*, **80**, 4607 (1958).

[3] Allen and Edens, *Org. Syntheses*, Coll. Vol. **3**, 732 (1955).

[4] Raphael, *Acetylenic Compounds in Organic Synthesis*, pp. 68–75, Academic Press, New York, 1955.

[5] Zakharkin, *Doklady Akad. Nauk S.S.S.R.*, **105**, 985 (1955) [*C.A.*, **50**, 11237a (1956)].

TETRAACETYLETHANE

(2,5-Hexanedione, 3,4-diacetyl-)

$$CH_3COCH_2COCH_3 \xrightarrow{\text{NaOH}} [CH_3COCHCOCH_3]Na$$

$$2[CH_3COCHCOCH_3]Na + I_2 \rightarrow$$
$$(CH_3CO)_2CHCH(COCH_3)_2 + 2NaI$$
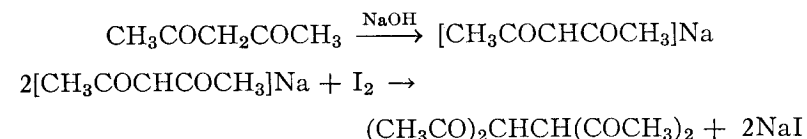
Submitted by ROBERT G. CHARLES.[1]
Checked by VIRGIL BOEKELHEIDE and HENRY FLEISCHER.

1. Procedure

A. *Sodium acetylacetonate.* A solution is prepared by dissolving 40 g. (1 mole) of sodium hydroxide in 50 ml. of water and adding to this 200 ml. of methanol. This solution is added, slowly with hand stirring, to 100 g. (1 mole) of acetylacetone (2,4-pentanedione) contained in a 500-ml. Erlenmeyer flask (Note 1). The creamy-white crystalline salt separates from

solution immediately. The flask is stoppered and cooled in ice (or in a refrigerator) for 2 hours or overnight. The sodium salt is collected on a Büchner funnel and washed with two small portions of cold methanol (Note 2). After the salt is air-dried, it is dried further either by allowing it to stand in a vacuum desiccator at room temperature or by heating it in a vacuum oven at 100° for 3 hours (Note 3). The anhydrous product, which is stable and can be stored indefinitely in a stoppered jar, weighs 70–80 g. (59–67%).

B. *Tetraacetylethane.* Sodium acetylacetonate is ground to a fine powder in a mortar, and 24.4 g. (0.2 mole) of the anhydrous material or 28.9 g. of the hydrate (Note 3) is weighed into a 1-l. Erlenmeyer flask. After 300 ml. of ether has been added, the suspension is stirred vigorously at room temperature with a magnetic stirrer. To the stirred mixture is added, dropwise from a separatory funnel, a solution of 25.4 g. (0.1 mole) of iodine dissolved in 300 ml. of ether. The rate of addition is maintained roughly constant by occasional adjustments of the stopcock, and the total addition is completed in about 2.5 hours. The reaction mixture is then poured into a large Erlenmeyer flask, and the ether is allowed to evaporate overnight at room temperature in a hood (Note 4). To the contents of the flask there is then added 500 ml. of water, and the mixture is allowed to stand for 2 hours. The remaining solid is collected on a Büchner funnel, washed several times with water, and finally dried in a vacuum desiccator. The yield (Note 5) of white solid, m.p. 185–188°, is 11–13 g. For purification, the product is taken up in 500–700 ml. of boiling methanol and the hot solution is filtered through a semi-fluted filter paper in a heated funnel. The filtrate is allowed to stand in the refrigerator for several hours. There is collected from the filtrate 8.0–11.7 g. (41–59%) of white crystals, m.p. 192–193° (cor.).

2. Notes

1. Eastman Practical Grade acetylacetone was found to be sufficiently pure for the preparation.

2. Washing with methanol decreases the yield somewhat but improves the purity of the product visibly. Additional, but less

pure, sodium salt can be obtained if desired by combining the filtrate and washings, and evaporating.

3. The sodium salt dried in a vacuum oven is anhydrous, while that dried in a vacuum desiccator was found to contain 15.6% water.

4. Some hazard is always involved in the evaporation of ether to dryness. To minimize the hazard, peroxide-free ether should be used and the evaporation conducted behind a shield. No difficulties have been encountered in the submitter's laboratory with a number of these preparations using previously unopened cans of anhydrous ether. If desired, the ether could be recovered by distillation. The explosive hazard is probably increased, however, by such a procedure.

5. The yield is essentially the same whether anhydrous or hydrated sodium acetylacetonate is used.

3. Methods of Preparation

Tetraacetylethane has been prepared previously both by the use of sodium metal [2] and of sodium hydride [3] with acetylacetone followed by addition of iodine. Also, the compound has been prepared in low yield by the reaction of diacetyl peroxide with acetylacetone [4] and by the electrolysis of acetylacetone in an alcohol-water solution.[2] The present method, although similar to those first mentioned, is somewhat more convenient and does not require anhydrous conditions.

[1] Westinghouse Research Laboratories, Pittsburgh 35, Pennsylvania.
[2] Mulliken, *Am. Chem. J.,* **15**, 523 (1893).
[3] Mosby, *J. Chem. Soc.,* **1957**, 3997.
[4] Kharasch, McBay, and Urry, *J. Am. Chem. Soc.,* **70**, 1269 (1948).

TETRACYANOETHYLENE

(Ethenetetracarbonitrile)

$$4CH_2(CN)_2 + 8Br_2 + KBr \rightarrow KBr[Br_2C(CN)_2]_4 + 8HBr$$

$$KBr[Br_2C(CN)_2]_4 + 4Cu \rightarrow$$

$$2(CN)_2C{=}C(CN)_2 + 4CuBr_2 + KBr$$
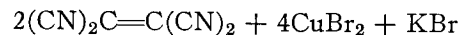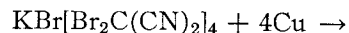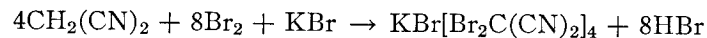
Submitted by R. A. Carboni.[1]
Checked by James Cason and Edwin R. Harris.

1. Procedure

Caution! Tetracyanoethylene slowly evolves hydrogen cyanide when exposed to moist air at room temperature. This material should be handled under a hood, and contact with the skin should be avoided. The first step in the preparation should also be carried out under a hood, since bromine is used.

A. *Dibromomalononitrile-potassium bromide complex.* In a 2-l. three-necked flask equipped with an efficient stirrer, a dropping funnel, and a thermometer are placed 900 ml. of cold water, 99 g. (1.5 moles) of malononitrile (Note 1), and 75 g. (0.63 mole) of potassium bromide. The flask is then placed in an ice-water bath, the stirrer is started, and the thermometer is adjusted to extend into the liquid but not into the path of the stirrer. When the temperature of the mixture has dropped to 5–10° (much solid crystallizes), 488 g. (158 ml. at 25°, 3.05 moles) of bromine is added over a period of 2.5 hours. The stirring is continued for an additional 2 hours, while the temperature is held at 5–10°. The precipitated solid complex is collected on a Büchner funnel, washed with 150 ml. of ice-cold water and sucked as dry as possible for about 1 hour (Notes 2 and 3). The grainy product is then dried to constant weight in a vacuum desiccator over phosphorus pentoxide, at the pressure obtained with an aspirator (Notes 4 and 5). The yield of light-yellow product is 324–340 g. (85–90%) (Note 3).

B. *Tetracyanoethylene.* A mixture of 254 g. (0.25 mole) of the dibromomalononitrile-potassium bromide salt and 1 l. of dry benzene is placed in a 2-l. three-necked flask fitted with a sealed mechanical stirrer and a reflux condenser. The stirrer is started (Note 6), and 100 g. (1.57 g.-atoms) of precipitated copper powder (Note 7) is added. The mixture is heated at reflux with constant stirring for 10–16 hours. The benzene layer becomes progressively deeper yellow as the reaction proceeds. At the end of the reaction period, the hot mixture is filtered by gravity, using a fluted paper. Most of the heavy solid is easily retained in the flask and is heated under reflux with 300 ml. of dry benzene, with stirring, for 30 minutes. Filtration of the hot mixture is carried out as before. Two 25-ml. portions of hot benzene are used to wash the precipitate and are decanted through the filter.

The combined filtrates are concentrated to approximately 350 ml. and cooled overnight at about 5°. The crystals are filtered by suction, washed with two 25-ml. portions of cold benzene, and dried in a vacuum desiccator (Note 8). The product weighs 35–40 g. (55–62%) and melts at 197–199° in a sealed capillary tube (Notes 9 and 10). This material is suitable for subsequent reactions if it is used within a day or two, although it gives somewhat lower yields than obtained with recrystallized material. This product may be purified, to yield material stable to storage, by recrystallization from nine times its weight of dry chlorobenzene (Note 11). There is recovered 85–90% of light beige crystals (Notes 12 and 13) melting at 199–200° (sealed capillary tube).

2. Notes

1. The malononitrile was obtained from the Winthrop-Stearns Corp., New York, N. Y., and melted at 30–31°.

2. The vapors of dibromomalononitrile-potassium bromide complex are irritating to the eyes and nose. The solid causes discoloration of the skin on contact. Manipulations should be carried out with gloves in a hood.

3. An additional few grams of product separates from the filtrate during this period, and a little more separates during 1-2

days' standing. This material amounts to 10–20 g. (2.5–5%) additional yield satisfactory for the next step.

4. The product may also be dried in a vacuum oven at 50°; however, the deposition of some free dibromomalononitrile on the walls of the oven renders this method of drying less advantageous. If an oil pump is used to evacuate the desiccator, it should be protected by an adequate trap containing solid sodium hydroxide.

5. It is essential that the complex be thoroughly dried; otherwise the yield of tetracyanoethylene in the subsequent step is materially decreased.

6. Dryness of the complex may be assured, and checked, by attaching a distillation head to the third neck of the flask and distilling benzene until the distillate has run clear for a few milliliters. If the apparatus and reagents were properly dried, only 10–20 ml. of slightly cloudy distillate should be observed.

7. The precipitated copper powder, Grade MD 98, was obtained from Metals Disintegrating Co., Elizabeth, New Jersey.

8. The crude product retains the odor characteristic of dibromomalononitrile and will stain the skin. Pure tetracyanoethylene is practically odorless.

9. The capillary is sealed in order to prevent sublimation; it should not be evacuated unless totally immersed in the heating bath, otherwise sublimation into the cooler part of the sealed capillary will occur.

10. A small additional quantity of less pure product may be obtained by heating the mother liquor with 20 g. of fresh copper powder for 1 hour with stirring, then filtering and concentrating the filtrate to about 100 ml. An equal volume of cyclohexane is added to the hot concentrate, and the mixture is cooled at about 5° for about 30 minutes. Following this procedure in one run, the checkers obtained a yield of 2.9 g. which was recrystallized from 26 g. of chlorobenzene to give 2.1 g. of unattractive material with a poor melting point.

11. The solubility of tetracyanoethylene in chlorobenzene apparently increases sharply as the boiling point of the solvent is approached. Thus the crystals should be extracted in boiling chlorobenzene. Chlorobenzene may be conveniently dried by distilling until the distillate no longer runs cloudy (azeotrope, b.p. 90°, 28.4% water).

12. The crystals, which are yellow when wet with chlorobenzene, become light-colored as the solvent is removed during drying.

13. If an especially good product is desired, the recrystallized material is sublimed at 130–140°/1 mm. A still better product with no trace of color may be obtained by subliming the recrystallized tetracyanoethylene through activated carbon. For example, 35 g. of tetracyanoethylene is placed in a glass thimble and covered with 20–25 g. of activated wood charcoal chips (4–8 mesh). The mouth of the thimble is covered with a coarse grade of filter paper which is held in place by wiring. The thimble is placed in a sublimer, and the sublimation is carried out at 1–2 mm. (bath temperature 175–190°). The tetracyanoethylene is recovered in 80–90% yield as a colorless, hard crystalline mass that melts at 201–202° (sealed tube).

3. Methods of Preparation

The procedure given above for the dibromomalononitrile-potassium bromide complex is essentially that of Ramberg and Wideqvist.[2] Tetracyanoethylene has also been prepared by passing malononitrile and chlorine through a hot tube at 400°.[3] The present procedure, based on that described by Cairns et al.,[3] appears to be the best preparative method. Tetracyanoethylene, the first example of a percyanoölefin, has shown exceptional reactivity in a number of addition reactions. For example, it is a very active dienophile, reacting rapidly at room temperature with many 1,3-dienes to give the corresponding Diels-Alder products.[4] With aromatic hydrocarbons, it forms π-complexes of characteristic colors ranging from yellow to green,[5] and it has been used as a color-forming reagent in paper chromatography of aromatic compounds.[6]

[1] Contribution No. 480 from Central Research Department, Experimental Station, E. I. du Pont de Nemours & Co. (Inc.), Wilmington, Delaware.

[2] Ramberg and Wideqvist, Arkiv Kemi, Mineral. Geol., 12A, No. 22 (1937).

[3] Cairns, Carboni, Coffman, Engelhardt, Heckert, Little, McGeer, McKusick, Middleton, Scribner, Theobald, and Winberg, J. Am. Chem. Soc., 80, 2775 (1958).

[4] Middleton, Heckert, Little, and Krespan, J. Am. Chem. Soc., 80, 2783 (1958).

[5] Merrifield and Phillips, J. Am. Chem. Soc., 80, 2778 (1958).

[6] Tarbell and Huang, J. Org. Chem., 24, 887 (1959).

p-TRICYANOVINYL-N,N-DIMETHYLANILINE

(Ethenetricarbonitrile, *p*-dimethylaminophenyl-)

$$(CH_3)_2N-\langle\ \rangle + (NC)_2C{=}C(CN)_2 \rightarrow$$

$$(CH_3)_2N-\langle\ \rangle-\underset{\underset{CN}{|}}{C}{=}C(CN)_2 + HCN$$
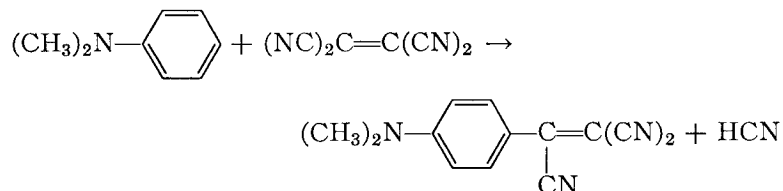
Submitted by B. C. McKusick and L. R. Melby.[1]
Checked by James Cason and Ralph J. Fessenden.

1. Procedure

Caution! Because hydrogen cyanide is formed in this reaction, all operations up to the recrystallization of the product should be carried out in a good hood. Contact of tetracyanoethylene with the skin should be avoided.

A solution of 26.6 g. (28 ml., 0.22 mole) of N,N-dimethylaniline in 65 ml. of dimethylformamide is placed in a 250-ml. beaker clamped about 30 cm. above the base of a ring stand. The beaker is provided with a mechanical stirrer and thermometer. An iron ring is attached to the ring stand below the beaker so that the temperature of the reaction mixture can be controlled by raising or lowering an ice bath or hot water bath. Recrystallized tetracyanoethylene [2] (25.6 g., 0.20 mole) is added in small portions over a period of about 5 minutes with good stirring. The rate of addition is such as to maintain the temperature at 45–50°, and occasional cooling with an ice bath may be necessary to keep the temperature within this range.

When all the tetracyanoethylene has been added, the reaction mixture is stirred at 45–50° for 10 minutes, and heat is supplied as needed by a water bath. *p*-Tricyanovinyl-N,N-dimethyl-aniline generally crystallizes out as a dark-blue solid during this period. At the end of the heating period, the mixture is chilled

in an ice bath for 30 minutes. The tricyanovinyl compound is collected on a Büchner funnel, pressed dry with the help of a filter dam, and washed successively with 20 ml. of methanol and 40 ml. of ether. It weighs 25–30 g. after being dried in air.

The crude product is purified by recrystallization from 160–180 ml. of acetic acid. The solution (Note 1) is allowed to cool slowly to room temperature, and *p*-tricyanovinyl-N,N-dimethyl-aniline is collected on a Büchner funnel and washed successively with 20 ml. of methanol and 40 ml. of ether. The product, 23–26 g. (52–58%), is obtained as dark-blue needles, m.p. 173–175° (Note 2).

2. Notes

1. The acetic acid solution is so deep a red color that it is necessary to hold the flask over a bright light in order to determine when all the solid has dissolved. The solution will dye the skin with a fast red color.

2. Although the crystals have a very dark blue appearance, the solutions are deep red; in acetone, λ_{max}. 517 mμ (ε 41,500).

3. Methods of Preparation

p-Tricyanovinyl-N,N-dimethylaniline has been prepared by adding hydrogen cyanide to *p*-dimethylaminobenzalmalono-nitrile and oxidizing the adduct.[3] The present procedure, an adaptation of one that has been published,[3] is the more convenient preparative method. It can be applied to a wide variety of secondary and tertiary aromatic amines to give *p*-tricyanovinyl-arylamines that, like the present one, are dyes.[3] Other types of aromatic compounds also condense with tetracyanoethylene in this manner. Thus one can obtain 4-tricyanovinyl-2,6-dimethyl-phenol from 2,6-dimethylphenol, 2-tricyanovinylpyrrole from pyrrole, and 9-tricyanovinylphenanthrene from phenanthrene.[4]

[1] Contribution No. 484 from Central Research Department, Experimental Station, E. I. du Pont de Nemours & Co. (Inc.), Wilmington, Delaware.

[2] Carboni, *Org. Syntheses*, **39**, 64 (1959).

[3] McKusick, Heckert, Cairns, Coffman, and Mower, *J. Am. Chem. Soc.*, **80**, 2806 (1958).

[4] Sausen, Engelhardt, and Middleton, *J. Am. Chem. Soc.*, **80**, 2815 (1958).

2,4,4-TRIMETHYLCYCLOPENTANONE

(Cyclopentanone, 2,4,4-trimethyl-)
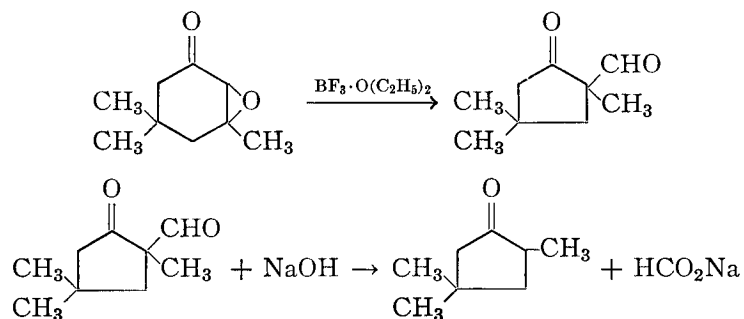
Submitted by GEORGE D. RYERSON, RICHARD L. WASSON, and
HERBERT O. HOUSE.[1]
Checked by JAMES CASON and RALPH J. FESSENDEN.

1. Procedure

In a 1-l. separatory funnel is placed a solution of 38.6 g. (0.25 mole) of isophorone oxide (Note 1) in 400 ml. of reagent grade benzene. To the solution is added 20 ml. (0.16 mole) of boron trifluoride etherate (Note 2). The resulting solution is mixed by swirling, allowed to stand for 30 minutes, then diluted with 100 ml. of ether and washed with 100 ml. of water (Note 3). The organic layer is shaken for 1–2 minutes with a solution of 40 g. (1.0 mole) of sodium hydroxide in 200 ml. of water (Note 4) and then washed with a second 100–ml. portion of water. The combined aqueous solutions are cooled briefly in running water and then extracted with two 50-ml. portions of ether. The ethereal extracts are added to the benzene-ether solution (Note 5), and the combined solution, after drying over anhydrous magnesium sulfate, is concentrated by distillation through a Claisen head. When the temperature of the distillate reaches about 80° (Note 6), the residual liquid is fractionally distilled (Note 7) under reduced pressure. The yield of 2,4,4-trimethylcyclopentanone, b.p.

61–62°/21 mm., n_D^{28} 1.4278–1.4288, is 17.7–19.8 g. (56–63%) (Note 8).

2. Notes

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

2. A practical grade of boron trifluoride etherate, purchased from Eastman Kodak Company, was redistilled before use. The pure etherate boils at 126°.

3. If the organic layer is dried over magnesium sulfate and fractionally distilled at this point, both 2,4,4-trimethylcyclopentanone and 2-formyl-2,4,4-trimethylcyclopentanone, b.p. 49–50° (2 mm.), n_D^{25} 1.4495, may be isolated. The pot residue from this distillation contains a small amount of the enol form of 3,5,5-trimethyl-1,2-cyclohexanedione which crystallizes from petroleum ether as white needles, m.p. 92–93°.

4. The specified period of shaking is sufficient to ensure complete deformylation of the intermediate β-keto aldehyde. Ordinarily, no difficulty is experienced with emulsification provided that the recommended quantity (or more) of ether is added to the reaction mixture.

5. Acidification of the residual aqueous solution followed by extraction with ether permits the isolation of about 1 g. of the enol form of 3,5,5-trimethyl-1,2-cyclohexanedione (see Note 3).

6. At this point about 150–200 ml. of liquid remains in the still pot. If the distillation is continued, the peppermint-like odor of the product, 2,4,4-trimethylcyclopentanone, can be detected in the distillate.

7. The submitters used a 24-cm. jacketed Vigreux column for this distillation. The checkers used a simple type of Podbielniak column, 50 cm. in length, with heated jacket and partial reflux head; after the last of the benzene had been distilled through the column, the following fractions were received:

Wt., g.	B.P./15 mm.	n_D^{28}
0.7	35–54°	1.4288
0.7	54–55°	1.4278
7.5	55°	1.4278
9.5	55°	1.4278
4.9	Residue, m.p. 80–90°	

Thus a rather good sample of product may be obtained without use of fractionating equipment.

8. If an appreciable quantity of higher-boiling material (consisting of 2-formyl-2,4,4-trimethylcyclopentanone; see Note 4) remains after the product has been collected, the residue should be dissolved in ether and shaken with aqueous sodium hydroxide as described in the procedure. After the ethereal extract has been dried over magnesium sulfate, distillation will permit the isolation of an additional quantity of 2,4,4-trimethylcyclopentanone.

3. Methods of Preparation

2,4,4-Trimethylcyclopentanone has been prepared by the oxidation of 1-hydroxy-2,4,4-trimethylcyclopentanecarboxylic acid with lead dioxide in sulfuric acid,[3] by the hydrogenation of 2,4,4-trimethyl-2-cyclopentenone,[4,5] by the Clemmensen reduction of dimethyldihydroresorcinol,[6,7] by the distillation of powdered 2,4,4-trimethyladipic acid with sodium hydroxide,[8] and by the saponification and decarboxylation of ethyl 2-keto-1,4,4-trimethylcylopentanecarboxylate.[9,10] The rearrangement of isophorone oxide [11] appears to represent the optimum combination of favorable yield and convenient procedure.

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

[2] Wasson and House, *Org. Syntheses*, **37**, 58 (1957).

[3] Wallach, *Ann.*, **414**, 296 (1918).

[4] Fjader, *Suomen Kemistilehti*, **5**, Suppl. 27 (1932) [*Chem. Zentr.*, **1932** I, 3172].

[5] Nazarov and Bukhmutskaya, *Bull. acad. sci. U.R.S.S., Classe sci. chim.*, **1947** 205 [*C.A.*, **42**, 7733 (1948)].

[6] Dey and Linstead, *J. Chem. Soc.*, **1935**, 1063.

[7] Auterinen, *Suomen Kemistilehti*, **10B**, 22 (1937) [*C.A.*, **32**, 509 (1938)].

[8] Birch and Johnson, *J. Chem. Soc.*, **1951**, 1493.

[9] Qudrati-Khuda and Mukherji, *J. Indian Chem. Soc.*, **23**, 435 (1946).

[10] Chakravarti, *J. Chem. Soc.*, **1947**, 1028.

[11] House and Wasson, *J. Am. Chem. Soc.*, **79**, 1488 (1957).

α,α,β-TRIPHENYLPROPIONITRILE

(Propionitrile, 2,2,3-triphenyl-)

$$(C_6H_5)_2CHCN \xrightarrow[\text{Liq. NH}_3]{\text{KNH}_2} [(C_6H_5)_2CCN]^-K^+$$

$$[(C_6H_5)_2CCN]^-K^+ + C_6H_5CH_2Cl \rightarrow$$

$$(C_6H_5)_2C\text{—}CH_2C_6H_5 + KCl$$
$$|$$
$$CN$$
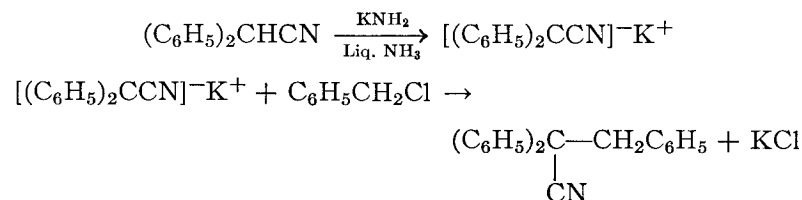
Submitted by C. R. Hauser and W. R. Dunnavant.[1]
Checked by Virgil Boekelheide and Donald R. Arnold.

1. Procedure

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

A suspension of potassium amide (0.23 mole) in liquid ammonia is prepared in a 1-l. three-necked flask equipped with an air condenser (without drying tube), a ball-sealed mechanical stirrer, and a dropping funnel. Commercial anhydrous liquid ammonia (500 ml.) is introduced into the flask from a cylinder through an inlet tube. To the stirred ammonia is added a small piece of potassium metal. After the appearance of a blue color, a few crystals (about 0.25 g.) of ferric nitrate hydrate are added, followed by small pieces of potassium (Note 1) until 9.0 g. (0.39 g.-atom) has been added. After all the potassium has been converted to the amide (Note 2), 44.6 g. (0.23 mole) of diphenyl-acetonitrile (Note 3) is added and the resulting greenish-brown solution is stirred for 5 minutes. To this is added, over 10 minutes, 30.5 g. (0.24 mole) of benzyl chloride (Note 4) in 100 ml. of anhydrous ether. The orange solution is stirred for 1 hour, and the ammonia is then evaporated on a steam bath as 300 ml. of anhydrous ether is being added. To the ether solution is added 300 ml. of water, whereupon the crude nitrile precipitates. The ether is then removed by distillation and the crude

nitrile is collected on a Büchner funnel. The yield of crude, light-tan α,α,β-triphenylpropionitrile is 64 g. (98–99%). The nitrile is dissolved in 1300 ml. of hot ethanol, treated with Norite, and filtered. The filtrate is held at room temperature overnight, and the product collected by filtration. A second crop is obtained by concentration of the mother liquor. The total yield of α,α,β-triphenylpropionitrile, m.p. 126.5–127.5°, is 62.2–65.5 g. (95–99% yield) (Note 5).

2. Notes

1. The potassium is cut in about 0.5-g. pieces, stored under kerosene, and blotted with filter paper before addition.

2. Conversion is indicated by the discharge of the deep-blue color. This generally requires about 20 minutes.

3. Diphenylacetonitrile supplied by the Eastman Kodak Company was used without purification.

4. Eastman Kodak Company practical grade benzyl chloride was vacuum-distilled; the fraction, b.p. 63°/12 mm., was used.

5. Under comparable conditions the corresponding alkylations of diphenylacetonitrile with α-phenethyl chloride and benzhydryl chloride have been effected to form 2,3,3-triphenylbutyronitrile and 2,2,3,3-tetraphenylpropionitrile in yields of 88 and 96% respectively.[2]

3. Methods of Preparation

The method used is that of Hauser and Brasen.[2]

The benzylation of diphenylacetonitrile with benzyl chloride to form α,α,β-triphenylpropionitrile has been previously effected in 83% yield by sodium ethoxide in ethanol,[3] in 67% yield by methylmagnesium iodide in ether,[4] and in unreported yield by sodium amide in ether.[5]

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

[2] Hauser and Brasen, *J. Am. Chem. Soc.*, **78**, 82 (1956).

[3] Neure, *Ann.*, **250**, 140 (1889).

[4] Sisido, Nozaki, and Kurihara, *J. Am. Chem. Soc.*, **72**, 2270 (1950).

[5] Ramart, *Bull. soc. chim. France*, [4] **35**, 196 (1924).

TRIPTYCENE

(9,10-*o*-Benzenoanthracene, 9,10-dihydro-)
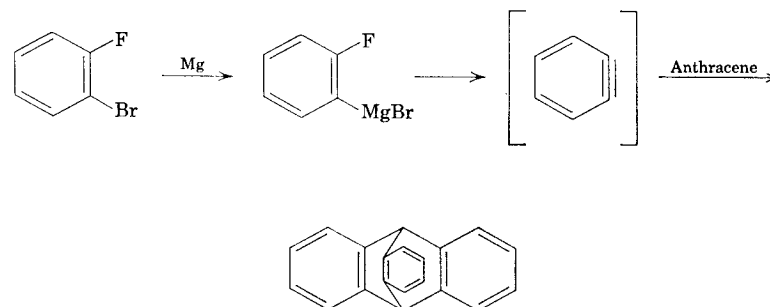
Submitted by GEORGE WITTIG.[1]
Checked by JOHN D. ROBERTS, M. C. CASERIO, E. S. JOHNSON, and L. SKATTEBØL.

1. Procedure

A 200-ml. three-necked flask, equipped with a ball-and-socket sealed mechanical stirrer, a pressure-compensated dropping funnel, and a reflux condenser connected to a mercury bubbler (Note 1), is charged with 0.8 g. (0.033 g.-atom) of magnesium turnings, 7.5 g. (0.042 mole) of anthracene, and 35 ml. of anhydrous tetrahydrofuran (Note 2). In the dropping funnel there is placed a solution of 5.26 g. (0.03 mole) of *o*-fluorobromobenzene (Note 3) in 15 ml. of tetrahydrofuran. The system is flushed with dry nitrogen for 30 minutes to remove air. The gas flow is then stopped in order to prevent extensive loss of tetrahydrofuran. The mixture is heated to and maintained at 60° (bath temperature), and one-quarter of the *o*-fluorobromobenzene solution is added with stirring. The appearance of a yellow color which evidences the start of reaction may not be observed immediately, and another quarter of the solution is then added dropwise over a period of about 45 minutes. When the reaction commences, the remaining solution is added dropwise over a period of 1 hour,

after which the mixture is refluxed gently for 90 minutes. The almost homogeneous dark-brown mixture is poured into 100 ml. of methanol, which precipitates much of the unreacted anthracene. Without filtering, the solvents are removed under reduced pressure and the yellow residue is treated with two 50-ml. portions of 5% hydrochloric acid, filtered, and vacuum-dried. The dry, yellow residue (10 g.) is dissolved in 45 ml. of hot xylene, then 5.0 g. (0.051 mole) of maleic anhydride is added. The mixture is refluxed for 20 minutes and set aside at room temperature for 2 hours. The maleic anhydride-anthracene adduct (about 9 g.) is removed by filtration, and the brown filtrate is refluxed for 2 hours with 80 ml. of 2N sodium hydroxide solution. When cool, the organic layer is separated, washed three times with 50-ml. portions of water (Note 4), and dried over calcium chloride. The solvent is removed at reduced pressure. The brown residue is dissolved in 70 ml. of carbon tetrachloride and chromatographed on 280 g. of acid-washed alumina, using 1 l. of the same solvent to elute. After evaporation of the solvent, there remains 2.4–2.9 g. of a yellow residue which is digested with two 10-ml. portions of pentane (Note 5). The residual crude triptycene is an almost white crystalline solid of melting point 240–248°. The yield is 2.14 g. (28%) (Note 6). Recrystallization of this material from cyclohexane gives pure white crystals of melting point 255–256°.

2. Notes

1. The mercury bubbler seals the system from the air. It is connected to the top of the reflux condenser by means of 8-mm. glass tubing more than 76 cm. high. The pressure in the system may be varied by adjusting the depth of the lower end of the tube. A constant stream of dry nitrogen may be substituted for the mercury bubbler, but this inevitably results in some loss of tetrahydrofuran.

2. Tetrahydrofuran may be purified by distillation from lithium aluminum hydride.

3. o-Fluorobromobenzene as supplied by the Aldrich Chemical Company, Milwaukee, Wisconsin, may be used without further purification.

4. Small amounts of sodium chloride may be added to facilitate separation of the phases.

5. The main impurity is a yellow oil which is readily soluble in pentane.

6. The checkers report a yield of 1.35–1.68 g. (18–22%) of triptycene of melting point 245–255°.

3. Methods of Preparation

Triptycene has been prepared by Bartlett and co-workers[2] in a seven-step synthesis.

[1] University of Tübingen, Tübingen, Germany.
[2] Bartlett, Ryan, and Cohen, *J. Am. Chem. Soc.*, **64**, 2649 (1942).

TRITHIOCARBODIGLYCOLIC ACID

(Carbonic acid, trithio-, bis[carboxymethyl] ester)

$$2KOH + H_2S \longrightarrow K_2S + 2H_2O$$

$$K_2S + CS_2 \longrightarrow (KS)_2CS$$

$$(KS)_2CS + 2ClCH_2CO_2K \longrightarrow (KO_2CCH_2S)_2CS$$

$$(KO_2CCH_2S)_2CS \xrightarrow{HCl} (HO_2CCH_2S)_2CS$$
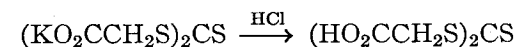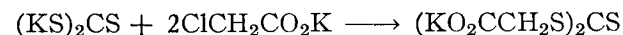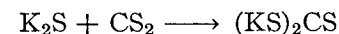
Submitted by R. E. Strube.[1]
Checked by John D. Roberts and Stanley L. Manatt.

1. Procedure

In a 300-ml. three-necked, round-bottomed flask equipped with a magnetic stirrer and a gas-inlet tube reaching below the surface of the liquid is placed a solution of 63 g. (1.1 moles) of potassium hydroxide (Note 1) in 100 ml. of water. The solution is cooled in ice, and hydrogen sulfide is bubbled through (Note 2) with stirring until the gain of weight is 33–34 g. (Note 3). The solution is then poured into a 3-l. three-necked, round-bottomed flask provided with a stirrer, a gas-inlet tube, a reflux condenser, and a

thermometer reaching into the liquid. The small flask is rinsed with 25 ml. of ice water and the rinsings added to the rest of the solution. Then 63 g. (1.1 moles) of potassium hydroxide is added and allowed to dissolve. The 3-l. flask is then well flushed with nitrogen and, at a temperature of about 30°, 76.0 g. (1.0 mole) of carbon disulfide (Note 4) is added at once. The mixture is stirred vigorously for 2 hours (Note 5) while nitrogen is passed through at a rate of about one bubble per second (Note 6) and the temperature is kept at 35–38° (Note 7). Then the gas supply is disconnected and the dark-red solution is cooled in an ice bath.

A solution of 189 g. (2.0 moles) of chloroacetic acid (Note 8) in 300 ml. of water is neutralized to litmus with a solution containing approximately 135 g. (2.41 moles) of potassium hydroxide in 300 ml. of water. The resulting potassium chloroacetate solution is placed in a dropping funnel and added to the stirred potassium thiocarbonate solution obtained above at such a rate that the temperature does not go above 40°. After the addition is complete, the stirring is continued for 1 hour at room temperature. Then 200 ml. of concentrated hydrochloric acid is added while the temperature is kept below 20° by cooling in an ice bath. Finally, the reaction mixture is stirred for 30 minutes at room temperature. The yellow precipitate is filtered and washed twice with 150-ml. portions of ice water. The crude material is dried under reduced pressure in a vacuum desiccator over calcium chloride to constant weight (about 2 days). The drying is expedited if the lumps are occasionally broken up. The yield of yellow product having m.p. 169–174° (uncor.) (Note 9) is 152–160 g. (67–71%).

2. Notes

1. Potassium hydroxide pellets, Mallinckrodt, 85% minimum KOH assay, were used.

2. A bubbler filled with mercury was placed between the gas cylinder and the gas-inlet tube. A good hood should be used throughout the procedure because hydrogen sulfide is toxic in minute concentrations.

3. Two to three hours is required to saturate the solution. The submitter used the same 3-l. flask to prepare the potassium

sulfide and to carry out the subsequent reaction. The checkers found the smaller flask more convenient for following the hydrogen sulfide uptake.

4. Carbon disulfide, Mallinckrodt, analytical grade reagent, was used.

5. The carbon disulfide layer usually disappears in about 45 minutes, but longer times may be required if the stirring is not effective.

6. Contact of the reaction mixture with atmospheric oxygen is to be avoided, but the gas flow should be kept slow enough to minimize loss of carbon disulfide. A bubbler filled with water was placed between the gas cylinder and the gas-inlet tube.

7. A water bath kept at 40–43° or an electrically heated mantle may be used.

8. Chloroacetic acid, m.p. 62–64°, Eastman Kodak, was used.

9. The submitter reports yields of 160–175 g. (71–77%) of product melting at 166–172°. Recrystallization from water gives 150–165 g. (66–73%) of material melting at 174–176° (cor.).

3. Methods of Preparation

Trithiocarbodiglycolic acid can be prepared by heating an aqueous solution of the alkali salts of thiocarbonylethoxythioglycolic acid,[2,3] by heating an aqueous solution of potassium methylxanthate and sodium monochloroacetate,[3] and by heating an aqueous solution of potassium thiocarbonate and sodium monochloroacetate.[3] The compound is also formed by heating an aqueous solution of potassium ethyltrithiocarbonate and sodium monochloroacetate,[4] and by heating an aqueous solution of thiocarbonylglycolic acid-thioglycolic acid with ammonia [5] or aniline.[6] The procedure described is adapted from that of Holmberg.[7]

[1] Department of Chemistry, Research Division, The Upjohn Company, Kalamazoo, Michigan.

[2] Holmberg, J. prakt. Chem., 71, 271 (1905).

[3] Biilmann, Ann., 348, 134 (1906).

[4] Holmberg, J. prakt. Chem., 75, 182 (1907).

[5] Ahlqvist, J. prakt. Chem., 99, 55 (1919).

[6] Holmberg, J. prakt. Chem., 84, 645 (1911).

[7] Holmberg, J. prakt. Chem., 71, 279 (1905).

SUBJECT INDEX

(This cumulative index comprises material from Volumes 30–39; for previous volumes see Collective Volumes 1, 2, and 3.)

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

ORGANIC SYNTHESES

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

VOLUME 39

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