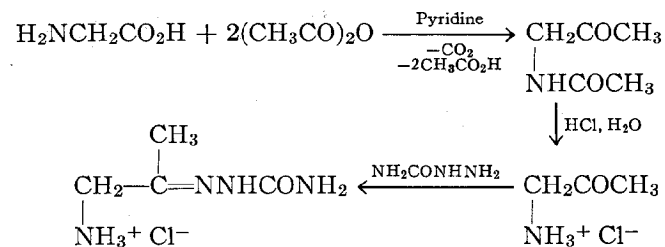


AMINOACETONE SEMICARBAZONE HYDROCHLORIDE

(Amino-2-propanone, semicarbazone hydrochloride)



Submitted by JOHN D. HEPWORTH¹

Checked by W. T. NOLAN and V. BOEKELHEIDE

1. Procedure

A. *Acetamidoacetone*. A mixture of 75.0 g. (1.0 mole) of glycine (Note 1), 475 g. (485 ml., 6 moles) of pyridine (Note 1), and 1190 g. (1.1 l., 11.67 moles) of acetic anhydride (Notes 1 and 2) is heated under reflux with stirring for 6 hours (Note 3) in a 3-l., three-necked, round-bottomed flask. The reflux condenser is replaced by one set for downward distillation, and the excess pyridine, acetic anhydride, and acetic acid are removed by distillation under reduced pressure. The residue is transferred to a simple distillation apparatus such as a Claisen flask and is distilled to give 80–90 g. (70–78%) of a pale yellow oil, b.p. 120–125° (1 mm.). This product is of satisfactory purity for use in step B.

B. *Aminoacetone hydrochloride*. A mixture of 175 ml. of concentrated hydrochloric acid and 175 ml. of water is added to 52 g. (0.45 mole) of the acetamidoacetone from step A contained in a 1-l. round-bottomed flask. The mixture is boiled under reflux under a nitrogen atmosphere (Note 4) for 6 hours. The resulting solution is concentrated using a flash evaporator held below 60° and with the condensation trap for solvent being

cooled by a dry ice-acetone bath. The dark red oily residue (40–45 g.) is satisfactory for use in step C (Note 5).

C. *Aminoacetone semicarbazone hydrochloride*. The product from step B is dissolved in 250 ml. of absolute alcohol in a 1-l. Erlenmeyer flask, and to this solution is added a solution of 48 g. of semicarbazide hydrochloride (Note 1) in 100 ml. of water. The mixture is allowed to stand at room temperature for 2 hours, the crystalline precipitate is collected by suction filtration, and the off-white product is washed on the filter with absolute alcohol. The crystals, after air-drying, amount to 54–58 g. (72–78%) and melt at 208–210°. The product is essentially pure and can be used for most purposes without further purification (Note 6).

2. Notes

1. The glycine, pyridine, acetic anhydride, and semicarbazide hydrochloride employed were of reagent grade and were used directly as supplied.

2. This ratio of pyridine to acetic anhydride has been found to be the most satisfactory.

3. It is necessary that the mixture actually boil under reflux or the yield may drop to 25–30%.

4. The checkers used high-purity nitrogen. If ordinary commercial nitrogen is employed, the oxygen should be removed by passing the gas through Fieser's solution.

5. Aminoacetone hydrochloride is very hygroscopic and is best stored as the semicarbazone. If the compound itself is desired, however, the dark red oil is dried under reduced pressure over phosphorus pentoxide. The resulting crystalline aminoacetone hydrochloride can be purified by dissolving it in absolute ethanol and precipitating it by the addition of dry ether.

6. For further purification, the semicarbazone hydrochloride may be recrystallized from aqueous ethanol to give colorless crystals, m.p. 212°.

3. Methods of Preparation

This preparation is based on the procedure used to synthesize 3-acetamido-2-butanone.² Aminoacetone hydrochloride has been

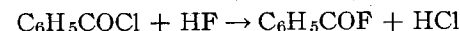
prepared from isopropylamine via the N,N-dichloroisopropylamine,³ from hexamethylenetetramine and chloroacetone,⁴ by reduction of nitroacetone⁵ or isontirosoacetone,⁶ and from phthalimidoacetone by acid hydrolysis,⁶ cited as the most convenient method of preparation.⁷ The semicarbazone has been prepared previously in the same manner.⁸

4. Merits of the Preparation

Aminoacetone is a versatile starting material for many syntheses, particularly for the preparation of heterocycles. The present procedure describes a convenient method for its preparation in a form suitable for storage. The aminoacetone can be generated from aminoacetone semicarbazone hydrochloride *in situ* as needed.

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BENZOYL FLUORIDE



Submitted by GEORGE A. OLAH and STEPHEN J. KUHN¹

Checked by JOHN A. DUPONT and WILLIAM D. EMMONS

1. Procedure

Caution! Anhydrous hydrogen fluoride is toxic and in contact with skin can cause serious burns. This preparation should be carried out in a well-ventilated hood. Rubber gloves and safety

goggles should be worn by the operator. In case of contact with hydrogen fluoride wash the affected skin area immediately with copious amounts of water, and apply a calcium gluconate paste (Note 1).

Hydrogen fluoride (50 g., 2.5 moles) is distilled from the cylinder through a polyethylene tube into a 250-ml. polyethylene transfer bottle which has been previously weighed and calibrated. A vent is provided during this process by inserting a large-gauge hypodermic needle through the bottle cap. No provision against atmospheric moisture is necessary. The bottle is cooled in a dry ice-acetone bath, and 45–50 ml. of liquid hydrogen fluoride is collected. The amount of liquid obtained can be determined by weight difference; however, since an excess of hydrogen fluoride is employed, the exact weight need not be determined. The time required for collection of the hydrogen fluoride can be appreciably shortened by placing the cylinder in a pan of warm water.

The reaction itself is carried out in a 1-l. polyolefin bottle (Note 2) or fused silica flask (Note 3) fitted with an inlet tube (Note 4) leading to the bottom of the reaction vessel and a reflux condenser which is connected to a hydrogen chloride absorber or which leads directly to the hood. A condenser suitable for work with anhydrous hydrogen fluoride can easily be prepared from a glass-jacketed polyolefin, Teflon®, silica, or copper tube (Note 5).

Benzoyl chloride (281 g., 2.0 moles) is placed in the reaction vessel, and the hydrogen fluoride gas is then introduced by its distillation from the transfer bottle through the inlet tube. Prior to this distillation the hypodermic needle is closed off by a metal cap. The hydrogen fluoride is added over a period of approximately 1 hour. Generally, external cooling is not needed, as the evaporating hydrogen chloride cools the reaction mixture. When the addition is completed, the reaction mixture is warmed to 30–40° and kept at this temperature for 1 hour. The mixture is then washed in an ordinary glass separatory funnel (Note 6) with 500 ml. of ice water in which 12.5 g. (0.2 mole) of boric acid is dissolved (Note 7). The organic layer is quickly separated, and to it are added 10 g. of anhydrous sodium fluoride and 10 g.

of anhydrous sodium sulfate (Note 7). The mixture is allowed to stand for 30 minutes and is then filtered and distilled through a short Vigreux column. The yield of benzoyl fluoride, b.p. 159–161°, n_D^{20} 1.4988 (Note 8), is 187–200 g. (75–80%).

2. Notes

1. An alternative treatment which has been used with good results at Rohm and Haas Company is, after thoroughly washing the exposed area with tap water, to soak the burned area in an ice-cold 0.2% solution of Hyamine 1622 (a product of Rohm and Haas Company) in 70% aqueous ethanol for 1 hour. It has also been stated that soaking the affected area with ice and water for 1 hour is almost as effective.²

2. Polyolefin bottles of suitable size are commercially available. One inconvenience occasionally observed with bottles which have not previously been in contact with hydrogen fluoride is the formation of a slight pink color in the reaction mixture, possibly due to the plasticizers. This coloration does not affect either the yields or the purity of the product, however, because the color is generally eliminated after the product is washed and treated with sodium fluoride.

3. No color problem exists when fused silica equipment, preferably with normal joints lubricated with a fluorinated grease, is used.

4. The inlet tube can be either polyolefin, Teflon®, fused silica, or copper.

5. Silica or copper gives much better heat transfer than do plastic tubes. The checkers found, however, that the use of a condenser was superfluous and that substitution of a simple polyethylene tube long enough to vent the off-gas away from the operator and apparatus was quite satisfactory.

6. Although some slight etching can take place, at this stage glass equipment is entirely safe, and no contamination of the product occurs.

7. The crude product contains hydrogen fluoride which is removed by the addition of boric acid to the wash water ($H_3BO_3 + 4HF \rightarrow HBF_4 + 3H_2O$). The sodium fluoride disposes of

any hydrogen fluoride remaining in the benzoyl fluoride ($\text{NaF} + \text{HF} \rightarrow \text{NaHF}_2$).

8. Benzoyl fluoride is a potent lachrymator and is undoubtedly toxic. It is advisable to rinse all glassware with acetone followed by 10% aqueous ammonia before removing the glassware from the hood.

3. Methods of Preparation

Benzoyl fluoride can also be prepared by the reaction of anhydrous hydrogen fluoride³⁻⁵ or potassium fluoride⁶ with benzoic anhydride and by the halogen exchange of benzoyl chloride with alkali fluorides, such as NaF ,⁷ KF ,⁶ KHF_2 ,⁸ Na_2SiF_6 ,⁹ or various other metal fluorides.¹⁰

4. Merits of the Preparation

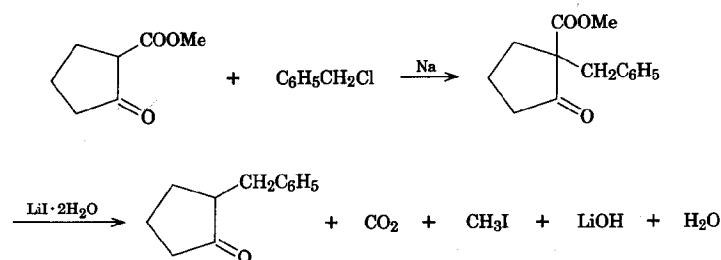
The described procedure, first applied by Colson and Fredenhagen,^{3,4} is useful for the preparation of a wide variety of acyl fluorides.⁵ The yields are normally 80–90%. Some examples of acyl fluorides prepared are listed in Table I. Benzoyl fluoride can also be employed as a convenient source of acetyl fluoride by reaction with acetic acid.¹¹

TABLE I

Product	B.P., °C.
Propionyl fluoride	43
<i>n</i> -Butyryl fluoride	69
Isobutyryl fluoride	61
Valeryl fluoride	90
Isovaleryl fluoride	81
Caproyl fluoride	122
Heptanoyl fluoride	40 (15 mm.)
Octanoyl fluoride	62 (15 mm.)
Pelargonyl fluoride	81 (15 mm.)
Decanoyl fluoride	92 (15 mm.)
Fluoroacetyl fluoride	54
Chloroacetyl fluoride	77
Dichloroacetyl fluoride	85
Trichloroacetyl fluoride	67
Bromoacetyl fluoride	104
Phthaloyl fluoride	84 (15 mm.)
Phenylacetyl fluoride	85 (15 mm.)

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2-BENZYL-CYCLOPENTANONE



Submitted by FRITZ ELSINGER¹

Checked by WILLIAM G. DAUBEN and W. TODD WIPKE

1. Procedure

A. *2-Benzyl-2-carbomethoxycyclopentanone*. A dry 2-l. three-necked flask is fitted with a Vibromischer stirrer (Note 1), a reflux condenser, and a 250-ml. dropping funnel with a pressure-equalizing side tube.² A nitrogen-inlet tube is connected to the top of the dropping funnel, and an outlet tube is placed on the

top of the condenser and connected to a mercury valve. The latter consists of a U-tube the bend of which is just filled with mercury.

To the flask are added 13.4 g. (0.58 mole) of clean sodium and 200 ml. of absolute toluene. The Vibromischer stirrer is activated, the toluene heated to reflux, and the agitation continued at this temperature until all the sodium is pulverized into a very fine sand. The agitation is ceased, and the solution is allowed to cool to room temperature. The nitrogen flow rate is increased, the Vibromischer stirrer is replaced with a conventional sealed mechanical stirrer with a Teflon® blade, and a solution of 85 g. (0.6 mole) of 2-carbomethoxycyclopentanone (Note 2) in 450 ml. of absolute benzene is placed in the addition funnel.

The stirrer is started, and the solution in the addition funnel is added over a 2-hour period without external heating (Note 3). After the addition is complete, the mixture is heated under reflux for 2.5 hours, at the end of which time the mixture has a pasty consistency. A solution of 106 g. (0.84 mole) of benzyl chloride in 100 ml. of dry benzene is added in one portion, the mixture heated under reflux for 14 hours, and the solution (Note 4) poured into 600 ml. of water. The benzene layer is separated, the aqueous layer extracted twice with ether, and the combined benzene-ether extract washed with 100 ml. of water and dried over anhydrous sodium sulfate. The solvent is removed under reduced pressure using a rotary evaporator, and the residual liquid distilled to yield 108–116 g. (81–86%) of colorless 2-benzyl-2-carbomethoxycyclopentanone, b.p. 126–128° (0.5 mm.) (Note 5).

B. 2-Benzylcyclopentanone. A mixture of 30 g. (0.177 mole) of lithium iodide dihydrate (Notes 6 and 7) and 140 ml. of dry 2,4,6-collidine (Note 8) in a 300-ml. three-necked flask fitted with a dropping funnel, a reflux condenser, and a nitrogen-inlet system (as in step A) is heated to reflux. As soon as all the lithium iodide has dissolved (Note 9), 30 g. (0.129 mole) of 2-benzyl-2-carbomethoxycyclopentanone dissolved in 30 ml. of 2,4,6-collidine (Note 10) is added to the boiling, faintly yellow solution; and during this process the solution turns darker in color and a precipitate forms (Note 11). Evolution of carbon dioxide

begins immediately, and its formation can be followed by passing the nitrogen flush through a saturated barium hydroxide solution. The mixture is heated under reflux and a nitrogen atmosphere for 19 hours, at the end of which time the evolution of carbon dioxide is very slow (Note 12).

The mixture is cooled and poured onto a mixture of 200 ml. of 6*N* hydrochloric acid, 200 ml. of ether, and 100 g. of ice. The residue in the flask is dissolved in a mixture of 6*N* hydrochloric acid and methylene chloride, and this mixture is added to the main reaction. The aqueous layer is separated and extracted with two 100-ml. portions of ether. The combined ethereal solution is washed once with 70 ml. of 6*N* hydrochloric acid, once with 2*N* sodium carbonate solution, twice with saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The solvent is removed under reduced pressure, and the residue is distilled to yield 16–17 g. (72–76%) of colorless 2-benzylcyclopentanone, b.p. 83–85° (0.3 mm.), 108–110° (0.75 mm.) (Note 13).

2. Notes

1. This stirring apparatus is available from Ag. für Chemie Apparatebau, Mannedorf, Zurich, Switzerland.

2. The submitter prepared the material from dimethyl adipate following the procedure published by Pickney³ for the diethyl ester. The checkers obtained their material by fractional distillation of mixed carbomethoxy- and carbethoxycyclopentanone available from Arapahoe Chemical Co., Boulder, Colorado.

3. If the 2-carbomethoxycyclopentanone is added in one portion, the yield of the product drops to 67%.

4. At the end of the reflux period, the reaction mixture is a nonviscous solution containing a white precipitate.

5. The semicarbazone melts at 168–170°.

6. Lithium iodide dihydrate is available from Fluka A.G., Buchs, S.G., Switzerland. The checkers used the trihydrate and, by means of a Dean Stark trap⁴ attached between the flask and the condenser, 1 mole of water was removed via azeotropic distillation with collidine.

7. In cases where a carbomethoxy group is desired to be selectively cleaved in the presence of a readily hydrolyzed ester group, such as an acetate of a secondary alcohol, anhydrous lithium iodide must be employed.⁵ In order to avoid partial decomposition of the salt to iodine, it is best dried by slowly heating it to 150° in a high vacuum. The solubility of anhydrous lithium iodide in boiling collidine or lutidine is slightly less than that of the dihydrate, but it still is adequate for the reaction. In the present case, the use of the anhydrous salt lowers the yield of the 2-benzylcyclopentanone to 67%, and a large amount of a product, believed to be a dimer, boiling around 200° (0.5 mm.) is obtained.

8. For the cleavage of less hindered esters, the lower-boiling 2,6-lutidine (b.p. 143°) can be used as the solvent.

9. The development of a small amount of iodine is difficult to avoid. The nitrogen atmosphere is essential to keep this salt decomposition to a minimum.

10. Methyl esters react more rapidly with lithium iodide than do ethyl esters, which in turn react more rapidly than esters of secondary alcohols. On the other hand, *t*-butyl esters are cleaved very readily with a catalytic amount of lithium iodide.

11. A precipitate remains throughout the reaction.

12. By using three mole equivalents of lithium iodide dihydrate, at the end of 6.5 hours of reflux a 77% yield of 2-benzylcyclopentanone is obtained.

13. The semicarbazone melts at 204–205°.

3. Methods of Preparation

This preparation of 2-benzyl-2-carbomethoxycyclopentanone is based on a procedure described by Baker and Leeds⁶ for the ethyl ester, and the methyl ester has not been previously prepared. The ethyl ester, also, has been prepared by the alkylation of 2-carbomethoxycyclopentanone with benzyl chloride in the presence of potassium hydroxide in acetaldehyde dipropylacetal.⁷ The preparation and isolation of the potassium salt of 2-carbomethoxycyclopentanone can be readily achieved in a very simple way

using aqueous alcoholic potassium hydroxide; by reaction of this salt with a variety of different halides in anhydrous media many 2-alkyl-2-carbomethoxycyclopentanones have been prepared.^{8, 9}

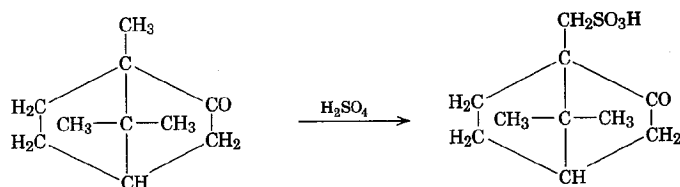
The preparation of 2-benzylcyclopentanone from 2-benzyl-2-carbomethoxycyclopentanone has not been previously reported. Starting with the ethyl ester, however, the compound has been prepared by heating the ester for many hours with concentrated hydrochloric acid.^{6, 10} The direct alkylation of cyclopentanone with benzyl chloride in the presence of sodium amide in liquid ammonia goes only in a poor yield.¹¹

4. Merits of the Preparation

This procedure illustrates a general method for the selective splitting of a carbomethoxy group in the presence of easily hydrolyzed esters of other alcohols, such as the easily hydrolyzed equatorial acetoxy group. The specificity of the reaction is not affected by steric hindrance, and a highly hindered methyl ester can be split in the presence of other less hindered esters of secondary alcohols. Normal alkaline saponification goes in exactly the opposite way.

The present case simply illustrates another utility of the ester cleavage reaction, *i.e.*, the cleavage of a β -keto ester with concomitant decarboxylation under only slightly basic conditions. The method should be particularly applicable to systems which are prone to undergo reverse Claisen reactions.

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D,L-10-CAMPHORSULFONIC ACID (REYCHLER'S ACID)

Submitted by PAUL D. BARTLETT and L. H. KNOX¹
 Checked by JOHN D. ROBERTS and DINSHAW PATEL

1. Procedure

In a 3-l., three-necked, round-bottomed flask fitted with a powerful slow-speed stirrer having a Teflon® blade, a 500-ml. dropping funnel, and a thermometer arranged to dip into the liquid is placed 588 g. (366 ml., 6 moles) of concentrated sulfuric acid. The flask is surrounded by an ice-salt mixture, the stirrer started, and 1216 g. (1170 ml., 12 moles) of acetic anhydride (Note 1) is added at such a rate that the temperature does not rise above 20° (Note 2). The separatory funnel is removed and 912 g. (6 moles) of coarsely powdered D,L-camphor is added (Note 3). The flask is then closed with a stopper and stirring is continued until the camphor is dissolved. The stirrer is replaced by a stopper, the ice bath allowed to melt, and the mixture left to stand for 36 hours (Note 4). The camphorsulfonic acid is collected on a suction filter and washed with ether (Note 5). After being dried in a vacuum desiccator at room temperature, the nearly white crystalline product weighs 530–580 g. (38–42%). It melts at 202–203° with rapid decomposition and is relatively pure (Note 6).

2. Notes

1. If the acetic anhydride is of a good commercial grade, it need not be redistilled.

2. When the temperature is allowed to rise above 20°, the acetic-sulfuric anhydride mixture acquires a yellow to orange color from which discolored crystals are subsequently deposited. The addition, which must be slow at first, requires 1–1.5 hours depending on the efficiency of the cooling bath.

3. The camphor employed is of the synthetic variety supplied by Howe and French, Boston. If an optically active product is desired, active natural camphor may be used.

4. The yields vary with the length of the crystallization period. After 16 hours the yield is 470 g. (34%). When the crystallization period is extended to 2 weeks, the yield is 615–655 g. (44–47%).

5. The checkers found the product to be very hygroscopic, in fact deliquescent, in a reasonably humid atmosphere. In such circumstances, it was preferable to decant the mother liquor from the crystals in the flask and to wash the solid by stirring it up with four 250-ml. portions of anhydrous ether, each washing being removed by decantation. The well-drained residual solid can then be transferred to a crystallizing dish and the ether removed by pumping under reduced pressure before the final drying in a vacuum desiccator over sulfuric acid.

6. The product can be purified with some loss by recrystallization from glacial acetic acid. About 60 g. of crude product dissolves in 90 ml. of acetic acid at 105° and gives a recovery of about 40 g. of purified material.

3. Method of Preparation

The procedure described is that of Reychler.²

4. Merits of the Preparation

D,L-10-Camphorsulfonic acid is used for the preparation of the corresponding chloride (p. 14). The optically active acid has been used widely for the resolution of basic compounds into optical antipodes.

1. Converse Memorial Laboratory, Harvard University, Cambridge, Massachusetts. Preparation was submitted November 1, 1939.

2. A. Reychler, *Bull. Soc. Chim.*, [3] **19**, 120 (1898); see also H. E. Armstrong and

1. The checker found it expedient to carry on the reaction in a 2-l. Pyrex[®] reaction kettle (Corning 6947), the large closure making the initial mixing of the solid reactant and the removal of the product much simpler.
2. The type of trap described in *Org. Syntheses*, Coll. Vol. 2, p. 4, is particularly useful.
3. The D,L-10-camphorsulfonic acid employed is the unrecrystallized product described on p. 12.
4. The initial mixing is conveniently made by turning the stirrer back and forth by hand.
5. The mixture does not usually become a clear solution because the product begins to crystallize. It is not difficult, however, to recognize yellow lumps of unreacted phosphorus pentachloride.
6. 10-Camphorsulfonyl chloride is rather rapidly hydrolyzed by warm water. The procedure here provides for complete hydrolysis of phosphorus oxychloride and excess phosphorus pentachloride without local heating and loss of product due to hydrolysis. For best results, the whole hydrolysis operation should be carried out quickly and steadily. It is well to have additional quantities of crushed ice on hand because the mixture may become quite hot if all of the ice added initially melts.
7. If the crude moist sulfonyl chloride is to be preserved, it must be thoroughly and reasonably rapidly dried. The checker found it very convenient to use a "freeze-drying" apparatus to remove the bulk of the moisture.
8. The submitters report that crystallization of the crude product from ligroin produces material of m.p. 83–84°. The sulfonyl chloride from (+)-camphorsulfonic acid has m.p. 67–68°.

3. Methods of Preparation

The procedure described here is adapted from that of Reychler.² The chloride may also be made from treatment of the acid with thionyl chloride.³

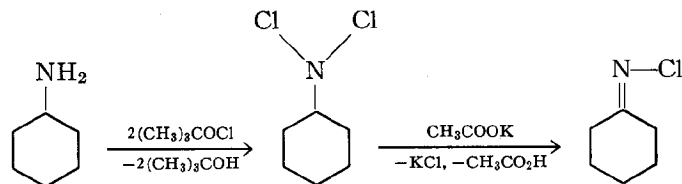
4. Merits of the Preparation

D,L-10-Camphorsulfonyl chloride may be oxidized to ketopininc acid (p. 55). The optically active forms of the sulfonyl chloride are useful for resolving alcohols and amines into optical antipodes.

1. Converse Memorial Laboratory, Harvard University, Cambridge, Massachusetts. Preparation was submitted November 1, 1939.
2. A. Reychler, *Bull. Soc. Chim.*, [3] **19**, 120 (1898).
3. S. Smiles and T. P. Hilditch, *J. Chem. Soc.*, **91**, 519 (1907); H. Sutherland and R. L. Shriner, *J. Am. Chem. Soc.*, **58**, 62 (1936); J. Read and R. A. Storey, *J. Chem. Soc.*, 2761 (1930).

N-CHLOROCYCLOHEXYLIDENEIMINE

(Cyclohexanimine, N-chloro-)



Submitted by G. H. ALT¹ and W. S. KNOWLES²
 Checked by P. M. BURKE and PETER YATES

1. Procedure

A. *N,N*-Dichlorocyclohexylamine (Note 1). In a 300-ml. three-necked flask fitted with stirrer, addition funnel, thermometer, and calcium chloride tube are placed 9.92 g. (0.10 mole) of cyclohexylamine (Note 2) and 50 ml. of dry benzene (Note 3), and the mixture is cooled to 0–5° by an ice bath. A solution of 24 g. (0.22

mole) of *t*-butyl hypochlorite³ in 50 ml. of dry benzene is added dropwise at such a rate that the temperature of the mixture does not exceed 10°. The mixture is allowed to come to room temperature and is then stirred for 1 hour, giving a solution of *N,N*-dichlorocyclohexylamine suitable for use in the next step.

B. *N*-Chlorocyclohexylideneimine. In a 500-ml. three-necked flask fitted with stirrer, addition funnel, thermometer, and reflux condenser fitted with a calcium chloride tube are placed 15 g. (0.15 mole) of potassium acetate (Note 4) and 100 ml. of absolute ethanol. The mixture is heated to reflux temperature, and, when the potassium acetate has dissolved, the *N,N*-dichlorocyclohexylamine solution is added at such a rate as to maintain reflux (Note 5). The reaction mixture is heated under reflux for an additional 3 hours, during which time potassium chloride precipitates. The mixture is cooled to room temperature, 200 ml. of ether and 100 ml. of water are added, and the resulting mixture is transferred to a 1-l. separatory funnel. The aqueous layer is separated and discarded. The ethereal layer is washed with three 100-ml. portions of water, three 50-ml. portions of 2*N* hydrochloric acid, and an additional three 100-ml. portions of water, the washings being discarded. The ethereal solution is dried over anhydrous calcium sulfate, and the solvent is removed at room temperature with a rotary evaporator and water aspirator. The residue is transferred to a 25-ml. distilling flask and fractionally distilled at reduced pressure through a short, vacuum-jacketed Vigreux column equipped with a Claisen type still head and a condenser through which ice water is circulated (Note 6). *N*-Chlorocyclohexylideneimine, b.p. 53–54° (3 mm.) (*Caution!* Note 7), n_D^{25} 1.506, is obtained in 48–69% yield (6.3–9.1 g.) (Note 8).

2. Notes

1. This method is essentially that of Baumgarten and Petersen.⁴
2. Eastman Organic Chemicals cyclohexylamine, white label grade, was redistilled prior to use.
3. Dried by azeotropic distillation: the first 10% of distillate is discarded.

4. Baker and Adamson, reagent grade.
5. The checkers found it preferable to maintain some external heating; otherwise the rate of addition had to be very rapid to maintain reflux.
6. Ice water is essential, and cooling of the receiver is recommended; otherwise considerable losses by evaporation occur.
7. The pot temperature should not be allowed to rise above 70° (the submitters used a hot-water bath at 75°), as a fume-off which may proceed with explosive violence is likely to occur. A nitrogen bubbler may be used to eliminate bumping. The distillation should be carried out behind a safety shield.
8. The compound decomposes slowly even under refrigeration and should be used within 24 hours of preparation. Analytically pure material, b.p. 36° (1.5 mm.), may be obtained by redistillation.

3. Methods of Preparation

N-Chlorocyclohexylideneimine has been prepared by the treatment of N,N-dichlorocyclohexylamine with triethylamine,⁵ potassium hydroxide,⁵ or potassium acetate⁶ and by reaction of chloramine with cyclohexanone⁷ or N-cyclohexylideneaniline.⁸

4. Merits of the Preparation

This method, which is an adaptation of that of Alt and Knowles,⁶ obviates the need to isolate the N,N-dichlorocyclohexylamine.

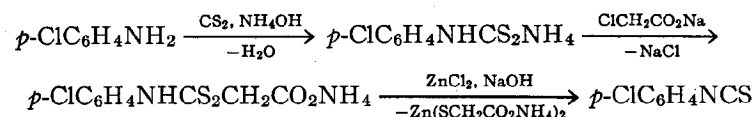
N-Chlorocyclohexylideneimine is of theoretical interest, being isoelectronic with the oxime tosylate. On treatment with 1 mole of base the imine undergoes a Neber-type rearrangement to the α -amino ketone⁶ and has been shown to be an intermediate in the rearrangement of N,N-dichlorocyclohexylamine to 2-amino-cyclohexanone.^{4, 6}

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p-CHLOROPHENYL ISOTHIOCYANATE

(Isothiocyanic acid, *p*-chlorophenyl ester)



Submitted by G. J. M. VAN DER KERK, C. W. PLUYGERS,
and G. DE VRIES¹

Checked by W. S. WADSWORTH, JR., and WILLIAM D. EMMONS

1. Procedure

Caution! p-Chlorophenyl isothiocyanate may cause severe dermatitis if allowed to come in contact with the skin. This preparation should be carried out in a good hood, and rubber gloves should be worn throughout.

In a 250-ml. round-bottomed flask fitted with mechanical stirrer, reflux condenser, and thermometer are placed 38.3 g. (0.30 mole) of *p*-chloroaniline (Note 1), 41 ml. (0.6 mole) of concentrated aqueous ammonia (sp. gr. 0.9), and 21 ml. (0.35 mole) of carbon disulfide. The mixture is stirred vigorously, and when it is heated to 30° the reaction starts. The temperature is maintained at 30–35° by external cooling (Note 2). The reaction mixture turns into a deep-red turbid solution within a few minutes, and then suddenly a heavy yellow precipitate of ammonium *p*-chlorophenyldithiocarbamate separates. To the mixture 15 ml. of water is added, and stirring is continued for 1 hour. The mixture is filtered with suction, and the residue is washed with

two 30-ml. portions of a 3% aqueous solution of ammonium chloride and with two 15-ml. portions of 96% ethanol.

The ammonium *p*-chlorophenyldithiocarbamate obtained is transferred immediately to a 1-l. beaker fitted with an efficient mechanical stirrer. Water (250 ml.) is added, and the temperature is raised to 30°. A solution of 28.4 g. (0.30 mole) of chloroacetic acid in 30 ml. of water is neutralized with sodium carbonate [18.6 g. (0.15 mole) of $\text{Na}_2\text{CO}_3 \cdot \text{H}_2\text{O}$ in 70 ml. of water] and is added to the well-stirred dithiocarbamate suspension over a 10-minute period (Note 3). In the beginning the suspension gradually becomes less viscous, but at the end of the addition it rapidly turns into a creamy mass. Another 250 ml. of water is added to facilitate stirring, which is continued for 1 hour after the addition at about 30°.

The creamy suspension is allowed to cool to room temperature, and the electrodes of a pH meter are inserted (Note 4). A solution of 20.5 g. (0.15 mole) of zinc chloride (Note 5) in 75 ml. of water is added dropwise with vigorous stirring over a period of 45 minutes, while the pH is maintained at 7 by the simultaneous dropwise addition of a 4*N* aqueous solution of sodium hydroxide (Note 6). The mixture is stirred for 1 hour and is then filtered with suction; the solid product is dried under reduced pressure over phosphorus pentoxide. The dry material is slurried with 200 ml. of petroleum ether (b.p. 30–60°), and the solvent is decanted. This process is repeated five times, and the combined extract is evaporated at reduced pressure. The yield of almost pure *p*-chlorophenyl isothiocyanate, obtained as a readily crystallizing oil with a pleasant anise-like odor, is 33–35 g. (65–68%), m.p. 44–45°. The product can be recrystallized from the minimum amount of ethanol at 50°.

2. Notes

1. A commercial grade (Eastman Organic Chemicals, white label) of *p*-chloroaniline was used without further purification.

2. The reaction is conveniently started by dipping the flask in a hot-water bath. The reaction temperature is easily maintained by occasional dipping of the flask in a cold-water bath.

3. Any free chloroacetic acid leads to the formation of *N-p*-chlorophenylrhodanine.

4. A Beckman pH meter (Model N) was used.

5. The anhydrous zinc chloride used was obtained from Baker and Adamson, reagent grade.

6. The pH must not drop below 7, although a slightly higher pH does no harm; addition of the zinc chloride in a shorter time lowers the yield.

3. Methods of Preparation

The procedure given here is essentially that described previously by the submitters.² *p*-Chlorophenyl isothiocyanate has been prepared from *sym*-di-*p*-chlorophenyl thiourea with iodine in alcoholic solution,³ from ammonium *p*-chlorophenyldithiocarbamate and lead nitrate⁴ [cf. also *Org. Syntheses*, Coll. Vol. 1 447 (1932)], by the action of thiophosgene on *p*-chloroaniline⁵ and from *p*-chloroaniline with thiocarbonyl tetrachloride in the presence of stannous chloride.⁶

4. Merits of the Preparation

The present method has the advantage that the whole process can be carried out in aqueous medium at low temperatures. The procedure is also attractive because of the reagents used and the relatively simple isolation procedure employed. The only restriction observed is that the formation of the aromatic dithiocarbamate must be possible.

Other isothiocyanates obtained by this method are: phenyl isothiocyanate (65%), *p*-phenylene diisothiocyanate (71%), *p*-acetylaminophenyl isothiocyanate (73%), *p*-ethoxyphenyl isothiocyanate (64%), and *p*-bromophenyl isothiocyanate (55%).

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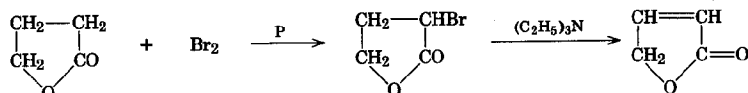
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γ -CROTONOLACTONE**($\Delta^{\alpha,\beta}$ -Butenolide)**

Submitted by CHARLES C. PRICE and JOSEPH M. JUDGE¹
 Checked by RICHARD F. ATKINSON and E. J. COREY

1. Procedure

Caution! Contact with α -bromo- γ -butyrolactone can cause severe eye and skin irritation. This preparation should be carried out in a good hood, and the operator should wear protective goggles and rubber gloves.

A. *α -Bromo- γ -butyrolactone.* In a 1-l., three-necked, round-bottomed flask equipped with a dropping funnel, sealed stirrer, and an efficient reflux condenser (Note 1) are placed 100 g. (1.16 moles) of redistilled γ -butyrolactone and 13.4 g. (0.43 g. atom) of red phosphorus. Over a half-hour interval, 195 g. (66.5 ml., 1.22 moles) of bromine is added, the mixture being stirred moderately and cooled by an ice bath.

This mixture is heated to 70° and an additional 195 g. (66.5 ml., 1.22 moles) of bromine added over a half-hour interval. After the bromine addition, the temperature is raised to 80° and the mixture held at that temperature for 3 hours. Air is blown into the cooled reaction until the excess bromine and hydrogen bromide are removed (Note 1). This process usually requires one hour (Note 2).

The aerated reaction mixture is heated to 80° and 25 ml. of water is added cautiously, with stirring. A vigorous reaction ensues, and upon cessation of the reaction an additional 300 ml. of water is added.

The reaction mixture of two layers and some solid residue is heated under reflux for 4 hours. Upon cooling, two layers again

appear. The product is extracted with two portions of ether (200 ml. each), and the extracts are dried over magnesium sulfate (Note 3). *Care should be taken since the α -bromolactone is a vesicant.*

The dried crude material is distilled, b.p. 125–127° (13 mm.), n_D^{25} 1.5030, yield 105 g. (55%).

B. *$\Delta^{\alpha,\beta}$ -Butenolide.* In a 500-ml. three-necked flask fitted with a mechanical stirrer, a reflux condenser, and a 250-ml. dropping funnel containing a solution of 61 g. (84.5 ml., 0.6 mole) of triethylamine in 70 ml. of dry diethyl ether, a solution of 83 g. (0.5 mole) of α -bromo- γ -butyrolactone and 200 ml. of dry diethyl ether is heated to reflux, with stirring. The amine solution is added, slowly, during 5 hours and the stirring under reflux continued for an additional 24 hours. The brown precipitate (40 g.) is removed by filtration. Most of the solvent is removed from the filtrate by evaporation, and the additional precipitate (8 g.) is removed. This precipitate is predominantly triethylamine hydrobromide. The liquid residue is distilled under reduced pressure and the $\Delta^{\alpha,\beta}$ -butenolide is collected at 107–109° (24 mm.); yield 25 g. (60%, 33% overall), m.p. 5°²⁻⁴ (Note 4).

2. Notes

1. A trap to catch the resulting bromine-hydrogen bromide vapors is desirable.

2. Pleninger⁵ reports that the product at this stage is α,γ -dibromobutyryl bromide.

3. Extraction with ether is necessary to separate the bromolactone efficiently.

4. The infrared spectrum of γ -crotonolactone shows two bands in the carbonyl region at 5.60 and 5.71 μ in carbon tetrachloride (5%) [shifted to 5.61 and 5.71 μ in chloroform (5%)] and carbon-carbon stretching absorption at 6.23 μ . The nuclear magnetic resonance spectrum shows olefinic peaks centered at 2.15 τ (pair of triplets) and 3.85 τ (pair of triplets), each due to one proton, and a two-proton triplet centered at 5.03 τ (in CCl₄).

In the ultraviolet, γ -crotonolactone shows end absorption at 205 m μ (ϵ ca. 11,000) and no maximum at higher wavelength.

Oxidation of this product by potassium permanganate affords 2,3-dihydroxy-4-butyrolactone.²

3. Methods of Preparation

The original preparation of γ -crotonolactone by Lespieau involved a five-step sequence from epichlorohydrin and sodium cyanide.² A recent detailed study of this procedure reported an overall yield of 25% for the lactone.³ Glattfeld⁴ used a shorter route from glycerol chlorohydrin and sodium cyanide; hydrolysis and distillation of the intermediate dihydroxy acid yielded γ -crotonolactone in 23% yield and β -hydroxy- γ -butyrolactone in 28% yield.⁴ The formation of γ -crotonolactone in 15% yield has also been reported from pyrolysis of 2,5-diacetoxy-2,5-dihydrofuran at 480–500°.⁶

The formation of α -bromo- γ -butyrolactone has been reported in 70% yield by uncatalyzed reaction of bromine at 160–170°,⁷ as well as by the catalyzed procedure used here.³

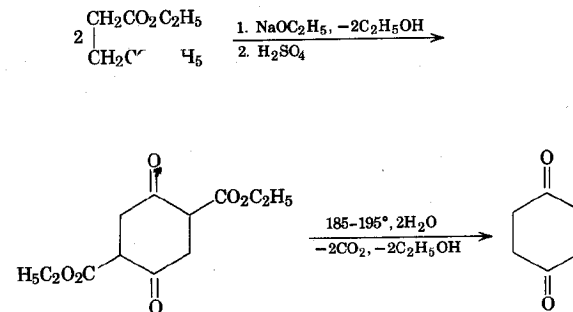
4. Merits of the Preparation

γ -Crotonolactone is the simplest example of the butenolide ring system, which occurs in many natural products. In view of the availability of butyrolactone, the present procedure represents the most convenient method of synthesis of the unsaturated lactone.

The dehydrohalogenation by a tertiary amine illustrates the utility of such amines for dehydrohalogenations which produce a double bond normally activated for attack by many bases.⁸

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1,4-CYCLOHEXANEDIONE



Submitted by ARNOLD T. NIELSEN and WAYNE R. CARPENTER¹
 Checked by WILLIAM G. DAUBEN and E. JOHN DEVINY

1. Procedure

A. 2,5-Dicarbethoxy-1,4-cyclohexanedione. A solution of sodium ethoxide is prepared by adding small pieces of sodium (92 g., 4 g. atoms) as rapidly as possible to 900 ml. of commercial absolute ethanol contained in a 3-l., three-necked, round-bottomed flask equipped with two stoppers and a reflux condenser fitted with a drying tube packed with calcium chloride and soda lime. The reaction is completed by heating the mixture under reflux for 3–4 hours (Note 1). To the hot solution is added diethyl succinate (348.4 g., 2 moles) (Note 2) in one portion (*Caution! Exothermic reaction*), and the mixture is heated under reflux by maintaining the original bath temperature for 24 hours. A thick pink-colored precipitate is formed almost immediately and remains throughout the reaction.

At the end of the 24-hour period, the ethanol is removed under reduced pressure on a steam bath. A 2*N* sulfuric acid solution (2 l.) is added to the warm residue, and the mixture is stirred vigorously for 3–4 hours (Note 3). The solid is removed by suction filtration and washed several times with water. The air-dried product is a pale-buff powder weighing 180–190 g., m.p. 126–128°. The solid is added to 1.5 l. of ethyl acetate, the mix-

ture is heated to boiling and is filtered rapidly while hot (Note 4). The filtrate is chilled, and it yields cream to pink-cream colored crystals of 2,5-dicarbethoxy-1,4-cyclohexanedione, 160–168 g., m.p. 126.5–128.5°. The filtrate is concentrated to one-tenth of its original volume in order to obtain a second crop of crystals, 5–7 g., m.p. 121–125°. The total yield is 165–175 g. (64–68%).

B. *1,4-Cyclohexanedione*. The purified 2,5-dicarbethoxy-1,4-cyclohexanedione (170 g., 0.66 mole) (Note 5) and 170 ml. of water are placed in a glass liner (vented) of a steel pressure vessel of 1.5-l. capacity (fitted with a pressure-release valve). The vessel is sealed, heated as rapidly as possible to 185–195°, and kept at this temperature for 10–15 minutes (Note 6). The reaction vessel is immediately removed from the heater, placed in a large tub of ice water, and cooled to room temperature. The gas pressure then is carefully released. The resulting yellow to orange liquid is transferred to a distillation flask with the aid of a minimum volume of ethanol, and most of the water and ethanol is removed under reduced pressure by means of a rotary evaporator. The flask is attached to a short heated column fitted with a short air condenser. The remainder of the water and ethanol is removed under reduced pressure, and the 1,4-cyclohexanedione is distilled, b.p. 130–133° (20 mm.). The product solidifies to a white to pale-yellow solid, m.p. 77–79°, yield 60–66 g. (81–89% yield from 2,5-dicarbethoxy-1,4-cyclohexanedione). The compound may be conveniently recrystallized from carbon tetrachloride (7 ml. per gram of dione); the purified product is obtained as white plates, m.p. 77–79° (90% recovery).

2. Notes

1. A heating bath containing a liquid heat exchanger such as hydrogenated cottonseed oil should be used. Employment of an electric heating mantle may cause extreme charring in the later stages of the reaction.

2. The diethyl succinate was obtained from Eastman Organic Chemicals and used without purification.

3. The lumps of the sodium salt of 2,5-dicarbethoxy-1,4-cyclohexanedione should be completely reacted before the filtration

step. If desired, the mixture may be stirred overnight at this point. The checkers found that in some runs a rock-like precipitate persisted on the bottom of the flask, and it had to be broken up manually by using a spatula with care.

4. A large fluted filter paper and a heated funnel are recommended for the filtration. The dark insoluble material which is removed by this process quickly fills the pores of the filter paper; more than one filter paper may be required. If a large amount of material remains in the filter, the material should be treated with additional ethyl acetate, the mixture filtered, and the filtrate combined with the first filtrate.

5. Use of unpurified ester results in a much lower yield of 1,4-cyclohexanedione.

6. An electrically heated pressure bomb, 4.5 in. in diameter, of 1.5-l. capacity, was employed (American Instrument Company, Model E 1143, cold-tested to 23,000 p.s.i.). About 90 minutes was required to raise the temperature from 25° to 185°.

3. Methods of Preparation

2,5-Dicarbethoxy-1,4-cyclohexanedione has been prepared by the self-condensation of diethyl succinate by use of sodium or sodium ethoxide catalyst (with or without a solvent)²⁻⁷ and by reaction of ethyl 4-bromo-3-ketobutanoate⁸ or ethyl 4-chloro-3-ketobutanoate^{9, 10} with sodium ethoxide in ethanol.

1,4-Cyclohexanedione has been prepared by hydrolysis and decarboxylation of 2,5-dicarbethoxy-1,4-cyclohexanedione by using concentrated sulfuric acid,¹¹ aqueous alcoholic phosphoric acid,¹² or water at 195–200°^{7, 13} and by peroxyvanadic acid oxidation of cyclohexanone.¹⁴

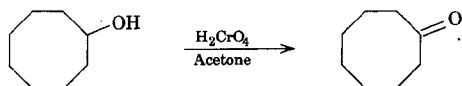
4. Merits of the Preparation

The present procedure is simpler than others previously described and gives equally good yields. It is easily adapted to the preparation of large quantities of either the diester or the diketone. It can be extended to the preparation of various alkylated 1,4-cyclohexanediones¹⁵ and bicyclic diketodicarboxylic esters such as diethyl bicyclo[2.2.2]octane-2,5-dione-1,4-dicarboxylate.^{16, 17} 1,4-Cyclohexanedione is a useful intermediate for

the preparation of 1,4-substituted cyclohexanes such as the di-oxime,¹⁸ diamine,¹⁹ 1,4-dichloro-1,4-dinitrosocyclohexane,²⁰ and 1,4-dinitrocyclohexane.²¹ It is also the precursor of 7,7,8,8-tetracyanoquinodimethan.²²

1. Organic Branch, Chemistry Division, U.S. Naval Ordnance Test Station, China Lake, California.
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CYCLOOCTANONE



Submitted by E. J. EISENBRAUN¹

Checked by E. J. COREY and ERNEST HAMANAKA

1. Procedure

The chromic acid oxidizing reagent is prepared by dissolving 67 g. of chromium trioxide in 125 ml. of distilled water. To this

solution is added 58 ml. of concentrated sulfuric acid (sp. gr. 1.84), and the salts which precipitate are dissolved by addition of a minimum quantity of distilled water; the total volume of the solution usually does not exceed 225 ml.

A solution of 64 g. (0.5 mole) of cyclooctanol (Note 1) in 1.25 l. of acetone (Note 1) is added to a 2-l. three-necked flask fitted with a long-stem dropping funnel, a thermometer, and a powerful mechanical stirrer (Note 2). The vigorously agitated solution is cooled in a water bath to about 20°. The chromic acid oxidizing reagent is added from the dropping funnel as a slow stream, and the rate of addition is adjusted so that the temperature of the reaction mixture does not rise above 35° (Note 3). The addition is continued until the characteristic orange color of the reagent persists for about 20 minutes (Notes 4 and 5). The volume of reagent added is about 120 ml.

The stirrer is removed, the mixture is decanted into a 2-l. round-bottomed flask, and the residual green salts are rinsed with two 70-ml. portions of acetone. The rinsings are added to the main acetone solution and additional oxidizing agent is added, if necessary, to ensure complete reaction. The stirrer is replaced and isopropyl alcohol is added dropwise until the excess chromic acid is destroyed (Note 6). In small portions and with caution there is added 63 g. of sodium bicarbonate, and the suspension is stirred vigorously until the pH of the reaction mixture tests neutral (Note 7). The suspension is filtered and the filter cake is washed with 25 ml. of acetone. The filtrate is concentrated by distillation through a 75-cm. length of Vigreux column until the pot temperature rises to 80° and a water film begins to develop in the lower portions of the distillation column (Note 8). The cooled pot residue (about 110 ml.) is transferred to a 1-l. separatory funnel, 500 ml. of saturated sodium chloride solution is added, and the mixture is extracted with two 150-ml. portions of ether. The ether extracts are combined, washed with a total of 25 ml. water in several portions, dried over anhydrous magnesium sulfate, filtered, and the ether distilled at atmospheric pressure. The pot residue is distilled under reduced pressure, b.p. 76–77° (10 mm.) (Note 9). The yield of cyclooctanone is 58–60 g. (92–96%), m.p. 40–42°.

An additional 2.2 g. (4%) of cyclooctanone may be obtained by addition of 250 ml. of water to the green salts formed during the reaction (Note 10), extraction of the mixture with ether, distillation of the ether, and addition of 12 ml. of acetone. To the acetone solution there is added sufficient chromic acid oxidizing reagent to permit the orange color of the reagent to persist (Note 11), and the mixture is processed as above.

2. Notes

1. Cyclooctanol is available from Aldrich Chemical Company, Inc. A redistilled solvent grade of acetone is satisfactory.

2. The submitter has also carried out this preparation starting from 2 moles of cyclooctanol. An 8-l. Pyrex® bottle, Corning No. 1595, is ideally suited for this scale. A round-bottomed flask is less desirable because it is necessary to see into the reaction vessel. Vigorous stirring is essential; a Lightnin Model L stirrer fitted with two 2-in., three-blade propellers is adequate for the larger-scale run. A cold-water bath for the 8-l. bottle may be conveniently constructed from an open-top 5-gallon solvent can by cutting a 1.5-cm. hole 5 cm. from the bottom and a 2.8-cm. hole 5 cm. from the top. These holes are respectively fitted with a rubber inlet tube ($1\frac{1}{16}$ in. O.D. by $\frac{3}{8}$ in. I.D.) and a rubber outlet tube ($1\frac{1}{2}$ in. O.D. by 1 in. I.D.). The rubber tubing fits directly in the holes without adapter or nipples.

3. The temperature is kept below 35° to avoid the use of a condenser.

4. The characteristic end point orange color can be demonstrated by addition of a slight excess of the chromic acid oxidizing reagent to a few milliliters of acetone containing a few drops of isopropyl alcohol.

5. The course of the reaction can conveniently be followed by gas chromatography. A sample of the reaction mixture is withdrawn at intervals, neutralized with solid sodium bicarbonate, dried over magnesium sulfate, and injected directly into a gas chromatography column consisting of 15% phenyldiethanolamine succinate (PDEAS) substrate coated on 60/80 mesh, acid-washed fire brick contained in a $\frac{1}{4}$ in. by 5 ft. spiral-shaped copper

tube. A Wilkens Instrument and Research, Inc., gas chromatography apparatus, Model A-90-P, operating at column temperature of 155°, 80 ml. per min. helium flow, was used. Complete separation of peaks (5.9 minutes for cyclooctanone, 7.0 minutes for cyclooctanol) is observed, and the reaction is considered complete when a peak for cyclooctanol can no longer be observed in the gas chromatogram.

6. The reaction mixture must be slightly acidic for the oxidation to proceed. On one occasion it was necessary to add a few drops of sulfuric acid to consume the oxidizing agent completely.

7. Calcium carbonate has also been used to remove residual acid.

8. If additional runs are contemplated, the recovered acetone may be used again.

9. A heat lamp may be used to prevent solidification during distillation.

10. The chromium salts formed during the oxidation are quite sticky and tend to occlude product as well as starting material.

11. The material freed from the chromium salts should be checked for completeness of reaction by gas chromatographic analysis to ensure the absence of starting material.

3. Methods of Preparation

Cyclooctanone has been prepared by distilling the calcium and thorium salts of azelaic acid,² by heating azelaic acid with barium oxide in the presence of iron,³ by the action of nitrous acid on 1-(aminomethyl)-cycloheptanol,⁴ by Dieckman cyclization of azelaic acid dimethyl ester⁴ and diethyl ester,⁵ and by ring expansion of cycloheptanone with diazomethane.^{6, 7}

4. Merits of the Preparation

This preparation illustrates a general and convenient way of oxidizing secondary alcohols to ketones in high yield. This procedure, usually called the Jones oxidation or oxidation by use of the Jones reagent,⁸ offers the advantage of almost instantaneous

oxidation of the alcohol under mild conditions. The reagent rarely attacks unsaturated centers; using this procedure an 81% yield of 2-cyclohexenone can be obtained from 2-cyclohexenol. The present example illustrates how this reagent can be utilized for a large-scale preparation. The major limitation of the reaction is the low solvent power of acetone.

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DIETHYL ACETAMIDOMALONATE¹

CORRECTION

The second sentence of the first paragraph of the procedure for the preparation of diethyl isonitrosomalonnate should read: "The flask is cooled in an ice bath, and a mixture of 57 ml. of glacial acetic acid and 81 ml. of water is added with stirring."

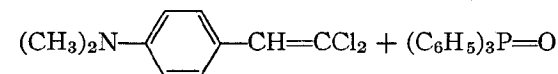
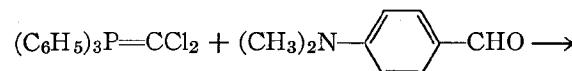
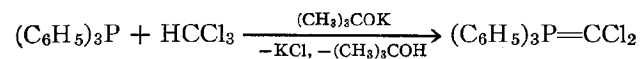
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DICHLOROMETHYLENETRIPHENYLPHOSPHORANE

[Phosphorane, (dichloromethylene) triphenyl-1]

AND

β,β -DICHLORO-*p*-DIMETHYLAMINOSTYRENE



Submitted by A. J. SPEZIALE, K. W. RATTS, and D. E. BISSING¹

Checked by WILLIAM E. PARHAM and L. DEAN EDWARDS

1. Procedure

A. *Potassium t-butoxide*. To 500 ml. of *t*-butyl alcohol (Note 1) in a 3-l. three-necked flask equipped with an efficient sealed stirrer, a nitrogen inlet (Note 2), a 500-ml. dropping funnel with a pressure-equalizing side tube (Note 3), and a reflux condenser there is added 20 g. (0.5 g. atom) of clean potassium metal. After the potassium has reacted, the condenser is replaced by a 12-in. distillation column and the excess *t*-butyl alcohol is removed by distillation until crystals begin to form in the solution. There is added 2 l. of dry heptane and the distillation is continued until the head temperature reaches 98° (Notes 4 and 5). The residual mixture is adjusted to a 1.5-l. volume by addition of dry heptane and the resulting slurry of potassium *t*-butoxide in heptane is cooled to 0–5° in an ice bath (Note 6).

B. *Dichloromethylenetriphenylphosphorane*. In one portion 131 g. (0.5 mole) of triphenylphosphine (Note 7) is added to the cooled suspension of potassium *t*-butoxide in heptane, and to the well-stirred mixture a solution of 59.5 g. (0.5 mole) of chloroform in 500 ml. of dry heptane is added dropwise over a period of

1 hour, maintaining the temperature below 5° and an atmosphere of purified nitrogen. The resulting stirred suspension is concentrated to a 750-ml. volume at reduced pressure and at 15–20° (Note 8).

C. β,β -Dichloro-*p*-dimethylaminostyrene. To the heptane suspension of the phosphorane there is added over a period of 30 minutes 74.5 g. (0.5 mole) of *p*-dimethylaminobenzaldehyde in six equal portions; the reaction temperature is maintained below 10°. The mixture is stirred for 2 hours in an ice bath, for an additional 5 hours at room temperature, and is then allowed to stand overnight. The precipitated phosphine oxide is filtered and the solvent is removed from the filtrate at 45–50° using a rotary evaporator. The resulting brown solid is recrystallized from methanol to yield 74–85 g. (68–79%) of crude olefin, m.p. 56–60°. The major impurity is unreacted triphenylphosphine.

The crude product is dissolved in absolute ethanol (10 ml. per gram of material), and a saturated solution of mercuric chloride (1 g. per 5 g. of crude olefin) in absolute ethanol is added (Note 9). The precipitate is filtered (Note 10) and washed with absolute ethanol. The filtrate is concentrated to half of its original volume (Note 11) and cooled in an ice bath. The yield of olefin is 42–60 g. (39–56%), m.p. 71–72°.

2. Notes

1. The *t*-butyl alcohol should be distilled from metallic sodium before use, care being taken to exclude moisture.
2. The nitrogen was purified by passing it through two wash bottles containing Fieser's solution² and single wash bottles containing concentrated sulfuric acid and solid anhydrous calcium chloride, respectively.
3. If available, it is more convenient to use a flask which also accommodates a thermometer extending into the reaction mixture.
4. It may be necessary to add more heptane during the distillation, as the slurry of potassium *t*-butoxide in heptane becomes very difficult to stir if the total volume is less than 1 liter.

5. About 2 hours is required for removal of all the excess *t*-butyl alcohol.

6. The potassium *t*-butoxide prepared in this manner is a 1:1 complex with *t*-butyl alcohol; neutralization equivalent calculated for $(\text{CH}_3)_3\text{COH} \cdot (\text{CH}_3)_3\text{COK}$, 186. Found: 184, 182. The complex can be isolated by simply removing the solvent at 20–25 mm. pressure on a steam bath. It can be stored for several months under a nitrogen atmosphere.

7. Triphenylphosphine was used as supplied by Eastman Organic Chemicals.

8. It is desirable to remove the *t*-butyl alcohol formed during the generation of dichlorocarbene because the *t*-butyl alcohol reacts with the phosphorane, thus lowering the yield of olefin. The evaporation is best accomplished with a vacuum pump (e.g., a Langdon pump) since the removal of *t*-butyl alcohol and heptane by water aspiration is very slow at this temperature. It is imperative that this step be accomplished as rapidly as possible and that the temperature be maintained below 20°. Although the suspension of phosphorane in heptane can be stored overnight under a nitrogen atmosphere, it is better to use it immediately.

9. Mercuric chloride forms with triphenylphosphine a double salt which is insoluble in ethanol.

10. It is necessary to use a fine or ultra-fine sintered-glass funnel or Whatman No. 1 filter paper because the precipitate is finely divided.

11. The checkers obtained better results by reducing the volume to one-third the original volume.

3. Methods of Preparation

Dichloromethylenetriphenylphosphorane has been prepared by the direct reaction of triphenylphosphine with carbon tetrachloride.³ 1,1-Dichloroethylenes have been prepared by dehydrochlorination of 1,1,1-trichloro compounds^{4–6} or by specialized methods applicable only to specific compounds.^{7, 8}

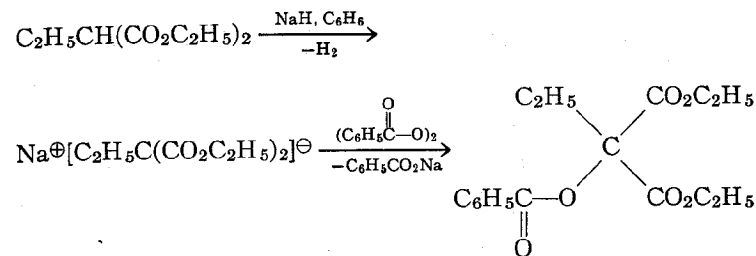
4. Merits of the Preparation

The procedure described illustrates a general method for the preparation of 1,1-dichloroethylenes. Dichloromethylenetriphenylphosphorane has been treated with a variety of aldehydes and ketones including *p*-nitrobenzaldehyde, 2,6-dichlorobenzaldehyde, cinnamaldehyde, lauraldehyde, acetaldehyde, cyclohexanone, and benzophenone to give the corresponding 1,1-dichloroethylene in good yield.⁹

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DIETHYL [O-BENZOYL]ETHYLTARTRONATE

(Malonic acid, ethylhydroxy-, diethyl ester, benzoate)



Submitted by E. H. LARSEN and S.-O. LAWESSON¹

Checked by M. R. MICHALEWICH and WILLIAM D. EMMONS

1. Procedure

Caution! This reaction should be carried out behind a safety screen. The solvent removal and product distillation steps should also be carried out behind a screen to minimize trouble if the product is contaminated with undetected peroxides. Benzoyl peroxide should be handled with caution because it is impact-sensitive.

To a 1-l., three-necked, round-bottomed flask is added 7.2 g. (0.15 mole) of a 50% dispersion of sodium hydride in mineral oil (Note 1). The sodium hydride is washed several times by decantation with dry ether and is then covered with 300 ml. of dry benzene (Note 2). The flask is equipped with dropping funnel, stirrer, and reflux condenser. Diethyl ethylmalonate (28.2 g., 0.15 mole) (Note 1) is added dropwise over a 5-minute period, and the reaction mixture is stirred for 2 hours until a clear solution forms. The solution is cooled in an ice bath, and 24.2 g. (0.1 mole) of benzoyl peroxide (Note 3) in 300 ml. of dry benzene is added dropwise over a 1-hour period with continuous stirring. After another 30 minutes, a peroxide test (Note 4) is made to ensure that all the peroxide has reacted.

The porridge-like mixture is then poured into 300 ml. of water and vigorously shaken in a 1-l. separatory funnel. The benzene

phase is separated, and the water phase is extracted three times with 100-ml. portions of ether. The combined extracts are washed until neutral and are dried over anhydrous sodium sulfate. The volatile solvents are evaporated at aspirator pressure, and the residue (Note 5) is distilled through a short Vigreux column. After a fore-run of diethyl ethylmalonate 23.3–24.1 g. (75–78%) of diethyl [O-benzoyl]ethyltartronate is obtained, b.p. 132° (0.1 mm.); n_D^{20} 1.4885.

2. Notes

1. The sodium hydride is obtained from Metal Hydrides Inc., Beverly, Massachusetts; the diethyl ethylmalonate from Eastman Organic Chemicals.

2. Reagent grade benzene was dried over calcium hydride prior to use.

3. The benzoyl peroxide is recrystallized from chloroform and methanol at room temperature. The checkers used the 96% purity commercial grade available from the Lucidol Division of Wallace and Tiernan without further purification.

4. A few drops of the reaction mixture are added to a dilute solution of sodium iodide in glacial acetic acid; if a brown ring is not formed, all peroxides have reacted.

5. A peroxide test on the residue is recommended before the distillation is begun.

3. Methods of Preparation

The present procedure is essentially that described by one of the submitters.²

4. Merits of the Preparation

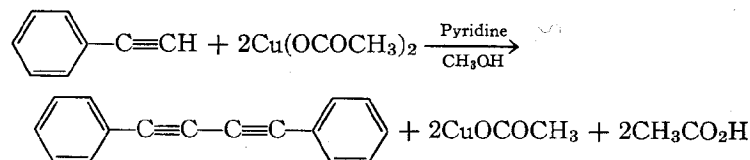
The reaction described is of considerable general utility for the preparation of benzoyloxy derivatives of β -carbonyl compounds. Thus O-benzoyl tartronates have been prepared, from which routes to diethyl tartronates and tartronic acids have been developed.² Ethyl benzoyloxy cyanoacetates have similarly been prepared and are of potential interest in connection with the chemistry of amino acid precursors.³ Similarly the benzoyloxy

group has been introduced into β -keto esters^{4, 5} and β -diketones.⁶ Also a new method for the preparation of acyloins was found.⁵ An extension of the method has led to certain types of benzoyloxy γ -keto esters⁷ and benzoyloxy δ -ketonitriles.⁸

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DIPHENYLDIACETYLENE

(Butadiyne, diphenyl-)



Submitted by I. D. CAMPBELL and G. EGLINTON¹

Checked by JOANNE GROVES and VIRGIL BOEKELHEIDE

1. Procedure

To a saturated solution of 5.5 g. (0.028 mole) of finely powdered cupric acetate monohydrate (Note 1) in 20 ml. of a 1:1 by volume pyridine-methanol mixture (Notes 2, 3, 4, and 5) contained in a 50-ml. round-bottomed flask fitted with a reflux condenser is added 2.0 g. (0.0196 mole) of phenylacetylene (Note 6). The deep-blue suspension becomes green when heated under reflux. After 1 hour of heating, the solution is cooled (Note 7) and added dropwise to 60 ml. of 18*N* sulfuric acid, with stirring and external cooling in an ice-salt freezing mixture (Note 8). The resulting white suspension is extracted with three 25-ml. portions of ether, and the combined ethereal extracts are washed with 15 ml. of

aqueous ethanolic silver nitrate solution (Note 9) to remove any unchanged phenylacetylene. The ether solution is then washed twice with water and dried over anhydrous magnesium sulfate. When the dried ether solution is concentrated under reduced pressure, a brown oil (1.81 g.) remains which solidifies on cooling.

The crude solid is purified by dissolving it in 50 ml. of petroleum ether (b.p. 40–60°) and introducing it on a short alumina column (15 g., Brockmann Activity 1 or an equivalent chromatographic alumina). The column is then eluted with 300 ml. of a 1:9 mixture of ether-petroleum ether (b.p. 40–60°). Concentration of the eluate leaves a solid which is recrystallized from aqueous ethanol to give 1.4–1.6 g. (70–80%) of diphenyldiacetylene as large colorless needles, m.p. 87–88° (Note 10).

2. Notes

1. Commercially available crystalline cupric acetate monohydrate was used. A large excess of cupric acetate does not improve the yield. Small catalytic amounts can be used if the cupric salt is continually regenerated by passage of oxygen through the reaction mixture, but the procedure is much slower.

2. A good grade of commercial pyridine was used. The reaction can also be carried out under anhydrous conditions (anhydrous cupric acetate, anhydrous methanol); then the pyridine is distilled from potassium hydroxide pellets. The yields are similar, and, in fact, water may be added as co-solvent if desired.

The solubility of anhydrous cupric acetate is ca. 2.3 g. per 100 ml. of pyridine, and that of the hydrate is ca. 1.6 g. per 100 ml. of pyridine. The solubility is much improved by the addition of methanol (solubility ca. 8.6 g. per 100 ml. of a 1:1 mixture of pyridine-methanol).

For high-dilution experiments, for example, the cyclization of α,ω -diynes, about 4 volumes of ether per volume of reagent solution can be added as entraining solvent without precipitation of the copper salt. A lower reaction temperature results.

3. Commercial grade methanol was used. Methanol is best avoided in experiments involving esters, as methanolysis has been encountered.²

4. It is apparently not essential that all the cupric acetate be in solution. Large volumes of solvent ensure complete solution but are inconvenient during isolation of the product.

5. Other solvent systems have been investigated. A base appears to be essential to remove the acetic acid formed; otherwise insoluble yellow precipitates of the cuprous derivative are obtained, which are only slowly oxidized to the required product.

6. Redistilled commercial phenylacetylene, titrating as 98% with silver nitrate-sodium hydroxide,³ was used.

7. The reaction can be followed by adding an aliquot to ethanolic silver nitrate solution (Note 9). The reaction is complete when no precipitate of the silver derivative is obtained. Also the disappearance of the infrared absorption band at 3300 cm^{-1} (3.03 μ) (ethynyl νCH) can be followed with carbon tetrachloride extracts of aliquots.

An 89% yield of diphenyldiacetylene was obtained when the reaction was allowed to proceed for 24 hours at room temperature (20°).

8. This is more convenient than removing the pyridine and the methanol by distillation.

9. The reagent is made by dissolving 3.5 g. of silver nitrate in 5 ml. of water and adding 10 ml. of ethanol.

10. The product may be contaminated by traces of the corresponding eneyne, *trans*-1,4-diphenyl-but-1-en-3-yne, formed by Straus coupling.⁴ This compound, however, has an ultraviolet absorption spectrum which differs markedly from that of diphenylbutadiene.⁵

3. Methods of Preparation

This compound has been prepared by air oxidation of the pre-formed cuprous salt.⁶ Another method uses aqueous cuprous chloride-ammonium chloride and an oxidant (e.g., oxygen).³

4. Merits of the Preparation

The reaction, "Glaser oxidative coupling," is a general one,⁷ but this particular technique is recommended for the more water-

insoluble ethynyl compounds, and also for the cyclization of α,ω -diynes,^{2, 8} where controlled dilution is required.

The cupric acetate-pyridine reagent provides a homogenous and basic reaction medium. The yields are high, and there is seldom precipitation of the cuprous derivative which may slow down the cuprous chloride-oxygen procedure.³

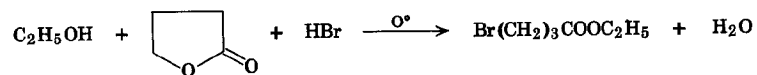
The rate of oxidative coupling is said to decrease with decreasing acidity of the ethynyl hydrogen.⁹ Thus oct-1-yne underwent only limited reaction after being heated with the reagent under reflux for 24 hours.

It is to be noted that cupric acetate has been used to oxidize other systems, for example, α -ketols, phenols, thiols, and nitroalkanes.

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ETHYL γ -BROMOBUTYRATE

(Butyric acid, γ -bromo-, ethyl ester)



Submitted by J. LAVETY and G. R. PROCTOR¹

Checked by IAN MORRISON and VIRGIL BOEKELHEIDE

1. Procedure

A solution of 200 g. (2.33 moles) of γ -butyrolactone (Note 1) in 375 ml. of absolute ethanol is cooled to 0° in an ice bath while a

stream of dry hydrogen bromide (Note 2) is introduced. The passage of gas is discontinued 1 hour after hydrogen bromide is seen to pass through the reaction mixture unchanged (Note 3).

The alcoholic solution of the product is kept for 24 hours at 0° and then poured into 1 l. of ice-cold water. The oily layer is separated, and the aqueous layer is extracted with two 100-ml. portions of ethyl bromide (Note 4). The combined oil and extracts is washed with ice-cold 2% potassium hydroxide solution, then with very dilute hydrochloric acid, and finally with water. The organic layer is dried over sodium sulfate, the solvent is removed under reduced pressure, and the residual crude ester is purified by distillation. The yield of ethyl γ -bromobutyrate, obtained as a colorless oil, b.p. 97-99° (25 mm.), n_D^{25} 1.4543, is 350-380 g. (77-84%) (Notes 5 and 6).

2. Notes

1. Technical grade γ -butyrolactone was employed.
2. The hydrogen bromide is made by burning together hydrogen and bromine. The apparatus is essentially that described previously.^{2, 3} The submitters found that standard ground-glass fittings can be used throughout, connected where necessary by Neoprene® tubing. The combustion tube is made by "butt-joining" two ground-glass sockets. The checkers used commercial hydrogen bromide from a cylinder which was connected to the reaction flask through a safety trap.
3. The time varies from 6 to 8 hours, and the increase in weight from 450 g. to 480 g. Using the commercial hydrogen bromide, the checkers found the time for saturation to be 3.5-4 hours.
4. The aqueous layer may be kept and used again in repeating the reaction.
5. In smaller runs, yields as high as 95% have been obtained.⁴
6. The product is best stored in dark bottles at 0°.

3. Methods of Preparation

The ester has been made from the corresponding acid which was obtained from the nitrile,⁵ but the present method is the

more practicable.^{4, 6} This procedure is an adaptation of the method used for the preparation of ethyl 2-bromocyclopentaneacetate.⁷

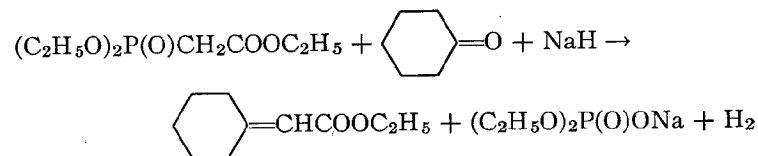
4. Merits of the Preparation

This is a simple procedure for preparing ethyl γ -bromobutyrate in good yield. Ethyl γ -bromobutyrate is used for adding chains of four carbons and has been particularly useful in syntheses of benzazepines.^{3, 6, 8, 9}

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ETHYL CYCLOHEXYLIDENEACETATE

(Δ^1 - α -Cyclohexaneacetic acid, ethyl ester)



Submitted by W. S. WADSWORTH, JR., and WILLIAM D. EMMONS¹
 Checked by WILLIAM E. PARHAM, R. M. DODSON, W. L. SALO,
 and J. N. WEMPLE

1. Procedure

A dry, 500-ml., three-necked flask equipped with stirrer, thermometer, condenser, and dropping funnel is purged with dry nitrogen and charged with 16 g. (0.33 mole) of a 50% dispersion

of sodium hydride in mineral oil (Note 1) and 100 ml. of dry benzene (Note 2). To this stirred mixture is added dropwise over a 45–50 minute period 74.7 g. (0.33 mole) of triethyl phosphonoacetate (Note 3). During the addition period the temperature is maintained at 30–35°, and cooling is employed if necessary (Note 4). Vigorous evolution of hydrogen is noted during this portion of the reaction. After addition of triethyl phosphonoacetate is completed, the mixture is stirred for 1 hour at room temperature to ensure complete reaction (Note 5). To this nearly clear solution is added dropwise over a 30–40 minute period 32.7 g. (0.33 mole) of cyclohexanone (Note 6). During the addition the temperature is maintained at 20–30° by appropriate cooling with an ice bath. After approximately one-half of the ketone is added, a gummy precipitate of sodium diethyl phosphate forms, which in some instances makes agitation difficult. The mixture is then heated at 60–65° for 15 minutes, during which time it is stirred without difficulty. The resulting product is cooled to 15–20°, and the mother liquor is decanted from the precipitate. This gummy precipitate is washed well by mixing it at 60° with several 25-ml. portions of benzene and decanting at 20° (Note 7). Benzene is distilled from the combined mother and wash liquors at atmospheric pressure. The product is distilled through a 20-cm. Vigreux column, and the mineral oil remains as pot residue after distillation is completed. Ethyl cyclohexylideneacetate (37–43 g., 67–77% yield) is collected at 48–49° (0.02 mm.), n_D^{25} 1.4755 (Note 8).

2. Notes

1. Sodium hydride, 50–51% in mineral oil, was supplied by Metal Hydrides Inc., Beverly, Massachusetts.
2. Reagent grade benzene is filtered from sodium hydride just before use.
3. Triethylphosphonoacetate may be obtained from the Aldrich Chemical Company and is distilled before use; b.p. 140° (10 mm.).
4. Temperatures above 40–50° are detrimental to the anion and must be avoided.
5. Approximately the stoichiometric quantity of hydrogen (7.4 l.) is evolved during preparation of the anion.

6. The cyclohexanone was obtained from Eastman Organic Chemicals and redistilled before use.

7. The submitters obtained the yields indicated by washing the gummy precipitate with two 25-ml. portions of benzene; the checkers observed that additional extraction at this point is required, and they recommend extraction with a total of four 25-ml. portions of warm benzene.

8. If an excess of sodium hydride has been used, the product contains varying amounts of the β,γ -isomer, ethyl cyclohexenylacetate. To ensure against the occurrence of this side reaction, a 5–10% excess of the phosphonate ester can be used.

3. Methods of Preparation

Esters of cyclohexylideneacetic acid have been prepared by the Reformatsky reaction followed by acylation and pyrolysis,² a laborious procedure giving low yields. The phosphonate carbanion procedure would appear to be the method of choice for preparation of these esters.

4. Merits of the Preparation

The phosphonate carbanion method is generally applicable to the synthesis of a wide variety of olefins.³ The synthesis complements the Wittig reaction in that the latter procedure is often unsatisfactory for preparation of olefins having an electron-withdrawing group adjacent to the double bond.⁴ Generally, any ketone or aldehyde can be used in the phosphonate carbanion synthesis, and yields of olefins comparable to that obtained with cyclohexanone are obtained. Although a variety of alkyl phosphonates can be employed, the present procedure is specific for phosphonates containing an electron-withdrawing group. The synthesis can be performed at room temperature or below, and product isolation is facilitated by simplified removal of the by-products, virtues which make this procedure of practical value.

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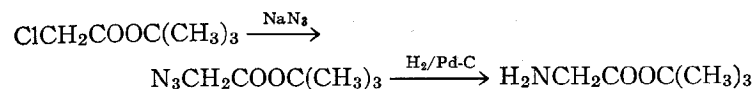
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H. Hoffman, H. G. Wippel, and G. Klahre, *Ber.*, **92**, 2499 (1959); H. Pommer, *Angew. Chem.*, **72**, 911 (1960); E. J. Seus and C. V. Wilson, *J. Org. Chem.*, **26**, 5243 (1961).

4. G. Wittig and W. Haag, *Ber.*, **88**, 1654 (1955).

GLYCINE *t*-BUTYL ESTER



Submitted by A. T. MOORE and H. N. RYDON¹

Checked by WILLIAM G. DAUBEN and JOHN A. HENNINGS

1. Procedure

A. *t*-Butyl azidoacetate. In a 300-ml. round-bottomed flask fitted with a reflux condenser are placed 30 g. (0.2 mole) of *t*-butyl chloroacetate (Note 1), 24 g. (0.37 mole) of sodium azide, and 90 ml. of 60% (v./v.) acetone-water. The heterogeneous mixture (two liquid phases and a solid phase) is heated under reflux on a steam bath for 18 hours, the acetone distilled, and 15 ml. of water added (Note 2). The mixture is transferred to a separatory funnel, the layers separated, and the lower aqueous layer extracted twice with 25-ml. portions of ether. The ethereal extracts are added to the original upper layer, and the solution is dried over anhydrous sodium sulfate. The ether is distilled, and the residual oil is fractionated under reduced pressure (Note 3), the fraction boiling from 33–41° (1 mm.) being collected; yield 29 g. (92%), n_D^{20} 1.4356 (Note 4).

B. *Glycine t*-butyl ester. In the center neck of a 500-ml. suction filtration flask is placed a gas-inlet tube which is connected to a nitrogen cylinder, and on the side arm of the flask there is attached an exit tube leading to a suitable ventilation duct. The flask is placed on a magnetic stirrer, and a solution of 28.9 g. (0.18 mole) of *t*-butyl azidoacetate in 150 ml. of methanol and 0.7 g. of 5% palladium-on-charcoal catalyst is added to the flask. A stream of nitrogen is swept over the surface of the stirred suspension for 5 minutes, the nitrogen cylinder is replaced by a

hydrogen cylinder, and hydrogen is passed over the magnetically stirred mixture for 10 hours. The hydrogen is displaced from the flask by a sweeping with nitrogen, the catalyst is removed by filtration and is washed with 5 ml. of methanol. The filtrate is transferred to a 500-ml. Erlenmeyer flask, 15 g. (0.18 mole) of phosphorous acid is added, and the mixture is warmed gently to dissolve the phosphorous acid. The solution is cooled to room temperature (Note 5), 150 ml. of ether is added slowly, and the solution is cooled at 0° for 12 hours. The precipitated glycine *t*-butyl ester phosphite is filtered, washed with ether, and dried in a vacuum oven at 70°, yield 29–32 g. (75–82%), m.p. 144–147° (dec.) (Notes 6 and 7).

To 50 ml. of a well-cooled 6*N* sodium hydroxide solution is added, with stirring, 32 g. (0.15 mole) of the phosphite salt. The stirring is continued until all the solid has dissolved. The solution is transferred to a 125-ml. separatory funnel, extracted with three 20-ml. portions of ether, and the combined extracts dried over anhydrous sodium sulfate. The drying agent is removed by filtration, the solvent removed under reduced pressure, and the glycine *t*-butyl ester distilled, b.p. 65–67° (20 mm.), n_D^{20} 1.4237, yield 14 g. (72%, based on phosphite salt). The overall yield from *t*-butyl chloroacetate is 50–55%.

2. Notes

1. The *t*-butyl chloroacetate was prepared from chloroacetyl chloride and *t*-butanol following the procedure of Baker.²

2. The water is added to dissolve any inorganic salts which are still not in solution.

3. Owing to the possibly explosive nature of the ester, the distillation was conducted behind a safety screen, using a water bath for the heat source and keeping the pressure as low as convenient.

4. The submitters reported a boiling point of 63–64° (5–6 mm.), n_D^{20} 1.4348. The literature values are b.p. 72–73° (13 mm.) and n_D^{25} 1.4332.³ The submitters also report that the reaction has been run safely on a 200-g. scale.

5. If the mixture sets solid upon cooling, the lumps of phosphite salt should be broken up during the addition of the ether.

6. The crystallization of the crude product from methanol-isopropyl ether gave pure phosphite salt, m.p. 154–157° (dec.).

7. Some *t*-butyl azidoacetate can be recovered by evaporation of the mother liquor. After removal of the methanol from the filtrate, the residual oil is dissolved in ether, washed with distilled water, the ether removed, and the residue fractionally distilled under reduced pressure (using proper precautions).

3. Methods of Preparation

This method is a modification of that developed by Vollmar and Dunn.³ Glycine *t*-butyl ester also has been prepared by the acid-catalyzed addition of *N*-benzyloxycarbonylglycine to isobutene, followed by catalytic hydrogenolysis of the resulting *N*-benzyloxycarbonylglycine *t*-butyl ester.⁴ The esters of other amino acids have been prepared directly by the isobutene method.⁵

4. Merits of the Preparation

Glycine *t*-butyl ester is a valuable intermediate for the preparation of peptides of glycine, since the labile *t*-butyl group can readily be removed by acid under conditions which do not affect the blocked amino grouping. The present method using *t*-butyl chloroacetate is superior to that using the bromo derivative,³ since chloride is cheaper to prepare, less lachrymatory and more easily separated, by fractional distillation, from the *t*-butyl azidoacetate. The method is also less cumbersome than the procedure using isobutene.

1. Department of Chemistry, University of Exeter, Exeter, England.

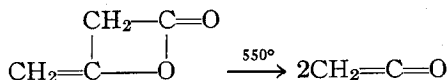
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KETENE



Submitted by S. ANDREADES and H. D. CARLSON¹
 Checked by R. DAVID CLARK, JAMES J. FUERHOLZER,
 and HENRY E. BAUMGARTEN

1. Procedure

Caution! Ketene (b.p. -41°) is a poisonous gas of the same order of toxicity as phosgene. All operations with ketene should be carried out in an efficient hood.

The pyrolysis apparatus consists of a vertical, electrically-heated Vycor[®] tube (25 mm. I.D.) packed with 6-mm. lengths of Pyrex[®] tubing (10 mm. O.D.) and mounted in an electric furnace about 45 cm. long (Notes 1 and 2). Attached to the top is a 100-ml. dropping funnel with a pressure-equalizing side arm² that has an inlet for nitrogen (Note 3). A thermocouple well inside the tube holds a movable thermocouple and extends to the bottom of the heated section (Note 4). The bottom of the reactor is fitted to a 500-ml. side-arm flask packed in ice. The side arm leads to two traps in series cooled in ice and to a final trap cooled in a bath of dry ice and acetone (Note 5).

The hottest part of the tube, which is near the middle of the heated section, is maintained at $550^\circ \pm 10^\circ$ while dry oxygen-free nitrogen is passed successively through a flowmeter and the tube at about 150 ml. per hr. for at least 30 minutes (Note 6). The dropping funnel is charged with 56 g. (0.67 mole) of diketene (Notes 7 and 8), which is then introduced into the hot tube at a rate of about 0.5 ml. per min. while the nitrogen flow continues. Essentially pure ketene (Note 9), yield 26–31 g. (46–55%) (Note 10), collects in the dry-ice trap as a colorless or nearly colorless liquid. The ketene is distilled directly from this trap for use in reactions.

If the ketene is not to be used at once, drying tubes should be

attached to the trap, which should then be stored at -80° . Ketene can be kept for as long as 2 weeks in this way, although some transformation to high-boiling material occurs (Note 11). However, pure ketene can be readily obtained from a partially decomposed mixture by simple distillation from the trap (Notes 11 and 12). *Caution! Do not store ketene under pressure, as an explosion may result.*

2. Notes

1. The furnace used by the submitters and checkers was an 1870-watt hinged type manufactured by the Hevi-Duty Electric Company, Milwaukee, Wisconsin; length 18 in.; inside diameter $2\frac{3}{8}$ in.; catalog No. M-2018. With the packing described, the total surface area in the packed tube is about 2000 cm.² In addition to this setup the checkers used a similar tube (20 mm. inside diameter) packed with $\frac{1}{8}$ -in. I.D. single-turn Pyrex[®] glass helices and inserted in a 550-watt furnace manufactured by the Hoskins Mfg. Co., Detroit, Michigan; length 12 in.; inside diameter $1\frac{1}{2}$ in.; catalog No. FD303A.

2. To prevent heat loss from the ends of the furnace opening, the ends are packed with Pyrex[®] glass wool or Fiberglas[®] insulation PF-105. In addition, the checkers capped each end of the furnace with a plate constructed from $\frac{1}{4}$ -in. Transite[®] sheet in which a hole just large enough for a loose sliding fit on the tube had been bored. The plate at the bottom of the furnace was held in place with a rubber stopper also bored to fit the tube, and the plate at the top of the furnace was held in place with an iron ring attached to the ring stand supporting the funnel.

3. The lower part of the barrel of the dropping funnel should be bent in such a way as to offset it from the path of the thermocouple to permit adjustment of the latter. The checkers used a 8-mm. glass tube bent for offset and fitted at the upper end with a nitrogen inlet and a standard-taper ground joint to permit attachment of funnels of various sizes.

4. Attachment of dropping funnel and thermocouple well to the pyrolysis tube may be made with a rubber stopper suitably bored.

5. The first two traps may be packed loosely with glass wool

to prevent mechanically entrained impurities (or aerosol) from passing through into the final trap. Omission of the glass wool may allow as much as 0.5–1.0 g. of colored material to be collected in the product. However, this colored impurity is easily removed by simple distillation. The checkers cooled the two traps in ice-ethanol.

6. The checkers passed the nitrogen through a gas absorption bottle filled to a depth of 10 cm. with concentrated sulfuric acid which had been calibrated roughly for flow rate. The rate of flow used was one bubble per 7 seconds (*ca.* 145 ml. per hr.) for the larger furnace, and one bubble per 10 seconds (*ca.* 100 ml. per hr.) for the smaller furnace.

7. Suitable diketene can be obtained from the Aldrich Chemical Company, Milwaukee, Wisconsin. If at all colored, this material should be distilled or sublimed before pyrolysis, for use of colored material may lead to a colored product. Distillation is easily carried out through use of the apparatus illustrated in Fig. 1. The impure diketene is placed in flask *A* and is cooled in ice and stirred with a magnetic stirrer. The Dewar trap is filled with dry ice and ethanol. Evacuation of the system with a vacuum pump is begun very carefully with appropriate upward adjustment of the pressure if necessary to prevent bumping and splashing. After the initial degassing and removal of low-boiling materials, the diketene distils smoothly (at 0.1–1.0 mm. pressure), collecting as a white solid on the cold surface of the Dewar trap. After the distillation is completed, the apparatus is partially disassembled and the dry ice and ethanol are poured out. As the diketene melts, it flows into flask *B*. The diketene should be stored under nitrogen in tightly stoppered brown bottles in a refrigerator or, better, below its freezing point of -6.5° , as otherwise it may slowly decompose.

8. Equally good results have been obtained with charges one-fourth to twice that of the present procedure.

9. The ketene obtained by simple distillation from the final trap is essentially pure. The purity can be determined by passing a weighed sample into 1*N* sodium hydroxide solution and titrating for excess base. The checkers found it very difficult to avoid entirely the collection of minute traces of high-boiling colored

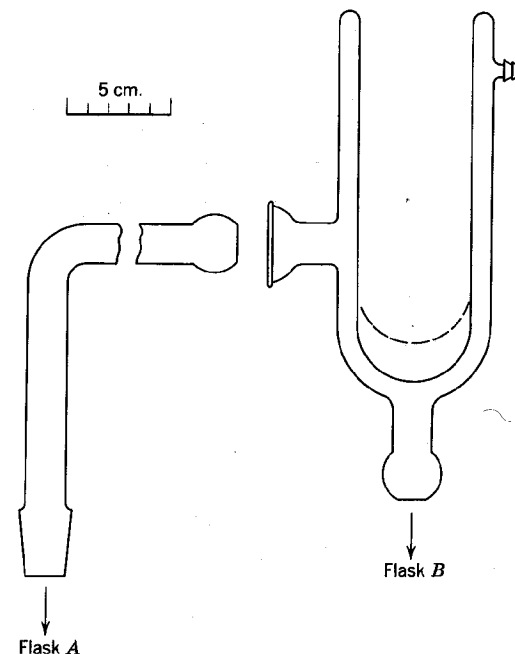


FIG. 1. Low-temperature distillation or evaporation apparatus. When solids are being collected, the Dewar flask bottom should be as indicated by the broken line.

impurities with the ketene. However, these impurities were easily removed by simple distillation of the ketene, just before use, from the original trap into a clean trap by warming the former in ice water and cooling the latter in dry ice and ethanol.

10. The checkers' yields were 54–66% for the larger furnace and 58–78% for the smaller furnace. The yield was found to be somewhat dependent on the rate of addition, with the rate specified in the procedure giving a good yield in a reasonable length of time. The checkers used an addition rate of 0.25–0.30 ml. per min. for the smaller furnace to obtain the yields cited.

11. Major impurities that collect on standing are all high-boiling, *e.g.*, diketene, b.p. 127° , and dehydroacetic acid, b.p. 270° . If the ketene has been stored long enough to allow a considerable portion of higher-boiling materials to accumulate, it is desirable to insert a trap cooled in an ice bath between the ketene-contain-

ing trap and the reaction vessel in order to minimize mechanical entrainment of the impurities. Repeated warming of the container to remove portions of the ketene naturally hastens transformation of the ketene to high-boiling materials.

12. The carbonaceous material that is deposited inside the pyrolysis tube is easily removed by passing a stream of oxygen through at about 550° after a thorough flushing with nitrogen.

3. Methods of Preparation

Ketene can be generated conveniently by pyrolysis of acetone in a hot tube³ or over a hot wire in a "ketene lamp,"⁴ or by pyrolysis of diketene in a hot tube.^{5, 6} Other methods of preparation have been summarized.³ It has been shown that diketene cracks quite cleanly to ketene,^{6, 7} although some allene and carbon dioxide are formed at the same time.⁷

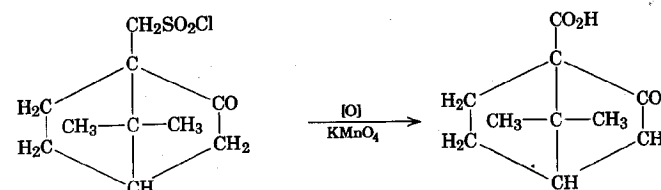
4. Merits of the Preparation

The two most convenient procedures for preparing ketene are the present one and the pyrolysis of acetone over a hot wire.⁴ The latter procedure can give ketene at a faster rate (0.45 mole per hr. versus 0.2 mole per hr.), but it takes considerable adjustment to get optimum conditions, and trouble is sometimes caused by the wire getting coated with carbon. Furthermore, because the efficiency of a given wire coil varies with time, passing through a maximum, frequent calibration of the apparatus is necessary. The present method is more reliable and is the method of choice when diketene is available.

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D,L-KETOPINIC ACID

(1-Apocamphanecarboxylic acid, 2-oxo-)



Submitted by PAUL D. BARTLETT and L. H. KNOX¹
Checked by JOHN D. ROBERTS

1. Procedure

A 4-l. beaker containing a solution of 100 g. (0.95 mole) of anhydrous sodium carbonate in 900 ml. of water is placed on a steam bath, provision being made for efficient mechanical stirring. The stirrer is started and, when the solution is hot, one-third of a solution of 100 g. (0.63 mole) of potassium permanganate in 600 ml. of hot water is added all at once, followed by a 34-g. portion of D,L-10-camphorsulfonyl chloride (Note 1). After an interval of 5-10 minutes, half the remaining permanganate is poured in, followed by 33 g. of the chloride. After a similar interval, the remaining permanganate solution and a final 33-g. portion of the chloride are added and heating is continued for an hour.

The excess permanganate is destroyed by adding a few milliliters of an acidified solution of sodium sulfite. The reaction mixture is cooled and made strongly acidic by cautious addition (foaming may occur) of 20% sulfuric acid. The mixture is heated, and the precipitated manganese dioxide is dissolved by stirring in powdered sodium sulfite (usually 70-80 g. is required). The resulting solution is cooled and extracted with one 200-ml., two 150-ml., and one 100-ml. portions of ether. The combined ether extracts are dried over anhydrous sodium sulfate and the bulk of the ether removed by distillation from a steam bath. The residue is evaporated in a crystallizing dish (Note 2). The crude acid (38-45 g.) is recrystallized from hot water. Considerable oiling may occur and 250-400 ml. of water is usually re-

quired to give complete solution. The yield of recrystallized acid is 28–32 g. (38–43%), m.p. 233–234° (Note 3).

2. Notes

1. The camphorsulfonyl chloride is the crude product obtained as described on p. 14. If it is not carefully dried, it should be oxidized reasonably promptly after its preparation. The oxidation is conveniently carried out in 100-g. portions. Several reactions can easily be carried out in parallel.

2. The checker found it convenient to use a rotary evaporator at this point.

3. An additional small crop of crystals may be obtained by concentration of the mother liquor. The checker observed m.p. 240–242°.

3. Methods of Preparation

D,L-Ketopinic acid has been prepared by oxidation of bornyl chloride with nitric acid at 20°² or with perbenzoic acid in acetic acid;³ from 10,10-dinitrocamphan-2-ol⁴ or apocamphan-2-ol-1-carboxylic acid⁵ with alkaline permanganate; and from the oxidation of 10-camphorchlorosulfoxide, obtained from 10-camphorsulfonyl chloride by the action of pyridine, with potassium permanganate.⁶ The present procedure represents a simplification of the latter and gives as high an overall yield.⁷

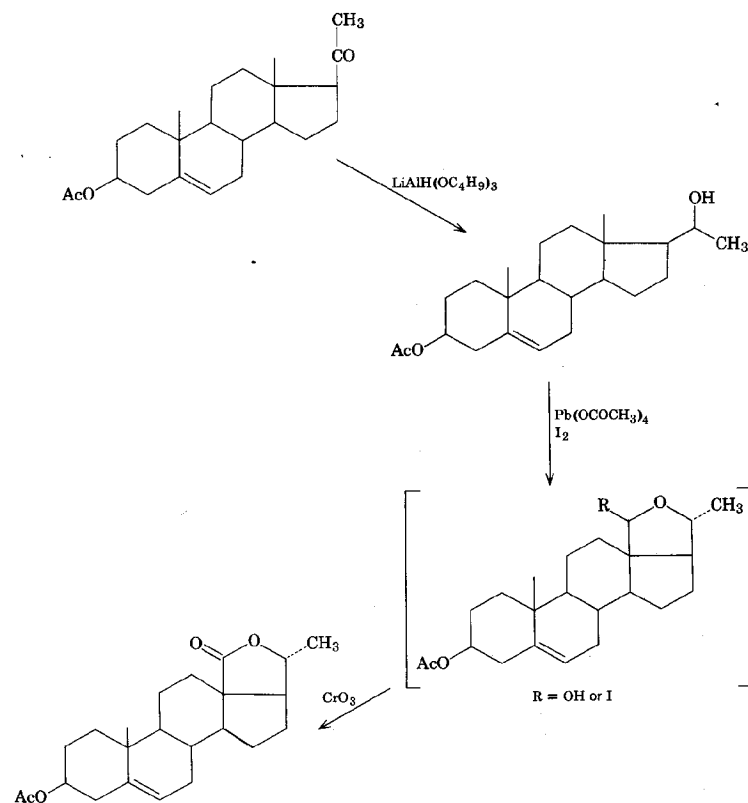
4. Merits of the Preparation

Ketopinic acid is of interest as a β -keto acid which fails to decarboxylate readily.⁸ It may be converted to apocamphane-1-carboxylic acid.⁷

1. Converse Memorial Laboratory, Harvard University, Cambridge, Massachusetts. Preparation was submitted November 1, 1939.
2. H. E. Armstrong, *J. Chem. Soc.*, **69**, 1397 (1896).
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18,20-LACTONE OF 3 β -ACETOXY-20 β -HYDROXY-5-PREGNENE-18-OIC ACID

(Pregn-5-en-18-oic acid, 3 β ,20 β -dihydroxy, 18,20-lactone, 3-acetate)



Submitted by K. HEUSLER, P. WIELAND, and CH. MEYSTRE¹
Checked by E. J. COREY and WILLIAM E. RUSSEY

1. Procedure

A. 3 β -Acetoxy-20 β -hydroxy-5-pregnene. In a 2-l. five-necked flask fitted with a mechanical stirrer, 250-ml. dropping funnel,

thermometer, nitrogen-inlet tube, and reflux condenser with calcium chloride tube is placed 750 ml. of anhydrous tetrahydrofuran (Note 1). The vessel is flushed with nitrogen, and 101.6 g. (0.4 mole) of lithium aluminum tri-*t*-butoxyhydride² (Note 2) is added. The suspension is cooled to about 2°, and 71.7 g. (0.2 mole) of pregnenolone acetate (Note 3) is added in one portion while stirring, the particles adhering to the wall of the flask being rinsed into the solution with an additional 50 ml. of tetrahydrofuran. The reaction mixture is stirred at 0–5° for 6 hours. A solution of 100 g. of ammonium sulfate in 150 ml. of water is added, with stirring, over a 15–20 minute period through the dropping funnel, the temperature of the reaction mixture being kept below 10° by efficient cooling with ice. A considerable quantity of hydrogen is evolved. There is added 20 g. of filter aid (Celite® or Hyflo Supercel®), the mixture is stirred for another 30 minutes, and it is finally filtered with suction through a layer of filter aid. The reaction vessel is rinsed and the filter residue thoroughly washed with 1.5 l. of tetrahydrofuran (Note 4). The filtrate is evaporated to dryness under reduced pressure. The crystalline residue is dissolved in 750 ml. of hot acetone, filtered (if necessary), and the solution is concentrated to a volume of about 200 ml. (crystallization may begin during this evaporation). The flask is kept overnight at 0° to –10° and the product isolated by suction filtration. The crystals are washed with 75 ml. of ice-cold acetone and dried at 60°. The yield of the product is 54–57 g. (75–79%), m.p. 161–164°,³ [α]_D²⁵ –74° (c 1.0, CHCl₃) (Note 5).

B. 3 β -Acetoxy-18-iodo- and 18-hydroxy-18,20 β -oxido-5-pregnene. In a 5-l. three-necked flask fitted with a mechanical stirrer, a thermometer, and a reflux condenser are placed 3 l. of cyclohexane (Note 6), 180 g. (ca. 0.37 mole) of commercial lead tetraacetate containing approximately 10% acetic acid (Note 7), 24 g. (0.095 mole) of iodine and 30 g. (0.083 mole) of 3 β -acetoxy-20 β -hydroxy-5-pregnene. The reaction mixture is stirred and heated to the boiling point by irradiation with a 1000-watt lamp (Note 8) from underneath. When the iodine color has disappeared (usually after about 60–90 minutes) (Note 9), the reaction mixture is cooled to room temperature, filtered with suction, and the

filter residue is rinsed with 600 ml. of cyclohexane. The filtrate is washed with two 500-ml. portions of 5% sodium thiosulfate solution and then with water. The combined aqueous solutions are extracted once with 500 ml. of ether. To the combined organic layers is added 6 ml. of pyridine, the solution is dried over sodium sulfate, filtered (Note 10), and the solvent evaporated under reduced pressure at a bath temperature of 35–40° (preferably by using a rotary evaporator). About 60 g. of an oily residue (Note 11), which is immediately oxidized (Note 12), is obtained.

C. Oxidation to the 18,20-lactone of 3 β -acetoxy-20 β -hydroxy-5-pregnene-18-oic acid. The above residue is dissolved in 600 ml. of acetone (Note 13), the solution is transferred to a 3-l. three-necked flask with a rigid mechanical stirrer, a dropping funnel, and a thermometer; the evaporation flask is rinsed with an additional 120 ml. of acetone. The solution is cooled to 0° to +5°, and 38.4 ml. of a chromic acid solution⁴ (prepared by mixing 13.3 g. of chromium trioxide and 11.5 ml. of concentrated sulfuric acid and carefully diluting the mixture to 50.0 ml. with water while cooling) is slowly added within 10 minutes from the dropping funnel. The mixture is stirred (Note 14) for another 30 minutes at 0° to +5°, and a solution of 270 g. of crystalline sodium acetate in 780 ml. of water is added. The dark green solution is transferred to a separatory funnel, and it is extracted once with 2.4 l. and once with 600 ml. of benzene. Each extract is washed twice with 600 ml. of half-saturated sodium chloride solution, dried over sodium sulfate, and the solvent is evaporated under reduced pressure. The combined semisolid residue (48–50 g.) is triturated with 50 ml. of ether and kept overnight at 0° to –10°. The crude product is filtered, and the filter residue is washed with pentane. The yield of crystalline lactone is 14–16 g. (45–52% based on pure 3 β -acetoxy-20 β -hydroxy-5-pregnene). For further purification the product is dissolved in 200 ml. of hot acetone, if necessary 250 mg. of charcoal is added, the mixture is brought to the boiling point on a steam bath, filtered through a layer of filter aid, and the filter residue is washed with warm acetone. The solution is concentrated on the steam bath to a volume of about 90 ml. During this operation,

crystallization begins. Then 150 ml. of hexane is added, the mixture is again concentrated to a volume of about 50–80 ml. with swirling, and finally kept at 0° overnight. A first crop of 12.0–13.5 g. (39–43%) of pure lactone, m.p. 201–206°, is obtained, $[\alpha]^{25}_D -44^\circ$ to -45° (c 1.0, CHCl_3). Concentration of the mother liquor yields a second crop of 0.3–2.7 g. of less pure lactone.

2. Notes

1. Tetrahydrofuran freshly distilled from lithium aluminum hydride should be used. A commercial product with a peroxide content giving a positive iodine test must be treated with about 0.3% of cuprous chloride (boiling for 30 minutes and distillation) before the addition of the hydride.

2. Obtained from Metal Hydrides Inc., Beverly, Massachusetts.

3. A commercial product, m.p. 142.5–148.5°; $[\alpha]^{20}_D +141.5^\circ$ (c 1.003, CHCl_3) was used.

4. Tetrahydrofuran free of peroxide, distilled from cuprous chloride, may be used.

5. The first crop of the product contains only a trace of the 20 α -epimer.³ The main portion of this compound is found in the mother liquor. Use of the material of a second crop for the subsequent steps is not recommended. The residue of the mother liquor can, however, be reoxidized to pregnenolone acetate by the method described in step C. By crystallization of the oxidation product of the mother liquor residue from methanol, 13–14 g. of pure pregnenolone acetate can be recovered.

6. Commercial product, redistilled. Small amounts of cyclohexene do not interfere.

7. Obtained from Fluka A. G., Buchs, S. G., Switzerland, and Arapahoe Chemical Co., Boulder, Colorado. Dry lead tetraacetate may also be used.

8. An ordinary 1000-watt lamp was used for heating as well as irradiation. The light reduces the induction period and accelerates the reaction. It is important that the solution be at reflux during the irradiation; an aluminum foil tent may be used to prevent excessive loss of energy from the light/heat source.

9. The disappearance of the iodine color is not indicative of the end of the reaction, since lead tetraacetate itself reacts with iodine under the reaction conditions giving lead diacetate, carbon dioxide, and methyl iodide. The reaction should be interrupted after 90 minutes even if a faint iodine color persists.

10. The filtrate contains labile iodine derivatives which in light and at room temperature give off iodine. If the solution is not concentrated immediately, it should be kept at 0° in the dark; but it should be processed within less than 4 hours because of the instability of the hemiacetal-type intermediate.

11. The oil contains considerable amounts of derivatives formed by reaction with the solvent, *e.g.*, cyclohexanol acetate, bicyclohexyl, and a number of high-boiling, iodine-containing substances. These by-products are removed only after oxidation.

12. It is important to oxidize the product as soon as possible because the crude 18,20-hemiacetal is unstable. In solution, in the presence of traces of acid, bimolecular anhydro products are formed which are stable to chromic acid oxidation and greatly diminish the yield of lactone.

13. Commercial acetone, boiled with 0.05% potassium permanganate for about 2 hours and distilled from potassium carbonate, was used.

14. The chromium sulfate tends to aggregate in large lumps. The stirrer should therefore be rigid and at least an inch away from the bottom of the flask.

3. Methods of Preparation

The preparation of the title lactone has been described by a multistep synthesis from holarrhimine.⁵ The method described in detail above is essentially an application of the "hypoiodite reaction" published by Ch. Meystre and co-workers.⁶ These authors also describe the isolation of the intermediate hemiacetal in pure form. Saturated lactones epimeric at C-20 have also been obtained by chromic acid oxidation of 18,20-dihydroxy compounds⁷ which were in turn prepared by treatment of 20-hydroxypregnanes with lead tetraacetate, acetolysis of the resulting 18,20 β -oxides, and hydrolysis. Saturated lactones of the

20 α - and 20 β -series were also obtained by photolysis of the corresponding 20-nitrites, hydrolysis, and oxidation.⁸

4. Merits of the Preparation

For the substitution of the angular methyl groups in steroids five methods are known: (a) homolysis of N-chloramines [Löffler-Freytag reaction⁹ (only C-18)]; (b) oxidation of alcohols with lead tetraacetate;¹⁰ (c) photolysis of nitrite esters;¹¹ (d) homolysis of hypochlorites;¹² (e) the "hypoiodite reaction."¹³

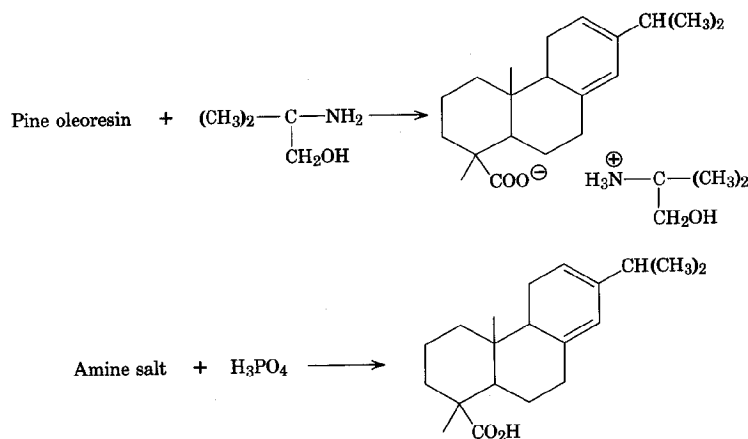
Of these methods the hypoiodite cleavage appears to be the simplest and most efficient one. It leads directly to compounds which are oxidized at the angular C-18 substituent to the aldehyde stage. In common with method (b), it has the advantage that an alcohol can be used directly as starting material, which under the reaction conditions is transformed into a derivative which is then homolytically cleaved; but, in contrast to method (b), the hypoiodite method is much less susceptible to steric effects, 20 β -alcohols being oxidized almost as efficiently as 20 α -alcohols. Methods (a), (c), and (d) require the formation of reactive derivatives in a separate step before homolysis. No special apparatus or special light source is needed for the hypoiodite reaction. Further applications and the scope of the reaction are discussed elsewhere.¹⁴

The lactone described can be used as starting material for the preparation of a number of 18-oxygenated steroids. Hydrolysis and Oppenauer oxidation^{5b, 6} leads to the 18,20-lactone of 3-oxo-20 β -hydroxy-4-pregnene-18-oic acid. This lactone is a suitable starting material for the preparation of 18-hydroxy- and 18-oxoprogesterone.¹⁵ On the other hand, microbiological oxidation leads to the corresponding 11 α -hydroxylactone¹⁶ which is a suitable starting material for the preparation of aldosterone.¹⁷

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LEVOPIMARIC ACID



Submitted by WINSTON D. LLOYD and GLEN W. HEDRICK¹
 Checked by WILLIAM G. DAUBEN and ROBERT M. COATES

1. Procedure

Pine oleoresin [1 kg. containing 260 g. (0.86 mole) of levopimaric acid] (Notes 1 and 2) is dissolved in 2 l. of acetone in a 4-l. beaker. A solution of 200 g. (2.2 moles) of 2-amino-2-methyl-1-propanol (Note 3) in 200 ml. of acetone is added as rapidly as possible with stirring. The pasty precipitate which forms almost immediately is collected by suction filtration and is pressed as dry as possible using a rubber dam (Note 4). The crude moist precipitate is returned to a 2-l. beaker and is dissolved in the minimum volume (~1 l.) of boiling methanol. The methanolic solution is cooled to 5° in a refrigerator and stirred occasionally to expedite crystallization. When the crystallization is completed, the solid is collected by suction filtration. The precipitate is redissolved in a minimum volume of boiling methanol (~1 l.) (Note 5), the solution concentrated to two-thirds its original volume (Note 6), cooled to 5°, and the amine salt allowed to

crystallize. The solid is filtered by suction, and the filter cake is air-dried to yield 68–78 g. (20–23% of the available levopimaric acid) of the 2-amino-2-methyl-1-propanol salt of levopimaric acid, $[\alpha]^{25}_{\text{D}} - 202^\circ$ (Notes 7 and 8). The recrystallization is repeated; approximately 0.8 l. of boiling methanol is used and then concentrated, the yield of amine salt is 41–46 g. (12–14% of the available levopimaric acid), $[\alpha]^{25}_{\text{D}} - 210^\circ$ (Note 9).

In a 1-l. separatory funnel there are first placed 400 ml. of ether and 75 ml. of 10% phosphoric acid (Note 10), and then the above amine salt is added (Note 11). The mixture is shaken vigorously for a few minutes, an additional 50 ml. of 10% phosphoric acid added, and the vigorous shaking continued until all the solid has disappeared. The ether layer is separated, washed twice with 100-ml. portions of water, and dried over anhydrous sodium sulfate. The drying agent is separated by filtration, the ether is removed at room temperature under reduced pressure using a rotary evaporator, and the residue dissolved in 40–60 ml. of boiling ethanol. The levopimaric acid is collected by suction filtration, yield 26–31 g. (10–12%), m.p. 147–150°, $[\alpha]^{25}_{\text{D}} - 265^\circ$ (Notes 12, 13, and 14).

2. Notes

1. The longleaf pine (*Pinus palustris*) oleoresin used was analyzed by the method of Lloyd and Hedrick² and was found to contain a total resin acid content of 660 g. The oleoresin used by the checkers was obtained from Shelton Naval Stores Co., Valdosta, Georgia. The oleoresin can also be obtained from the following sources: K. S. Varn and Co., Hoboken, Georgia; The Langdale Co., Valdosta, Georgia; Vidalia Gum Turpentine Co., Vidalia, Georgia; Stallworth Pine Products Co., Mobile, Alabama; Filtered Rosin Products Company, Baxley, Georgia; Taylor-Lowenstein and Co., Mobile, Alabama; and Nelio Chemicals, Inc., Jacksonville, Florida.

2. If any woody material remains undissolved, it should be removed by filtration of the acetone solution.

3. The 2-amino-2-methyl-1-propanol, m.p. 25–29°, N.E. 88.5–99.0, was obtained from the Commercial Solvents Corporation

and was used without further purification. The checkers obtained their material from Matheson Coleman and Bell Co.

4. The use of a rubber dam is essential in this step to effect the separation of the residual acetone. It is also beneficial to use a rubber dam in the other suction filtrations in this process.

5. If a clear solution is not obtained, the undissolved material should be removed by filtration.

6. Concentration of the solution at this point gives a major improvement in yield. Crystallization does not occur during this concentration step unless the solution is seeded.

7. All rotations were taken with a 2% methanolic solution.

8. If the rotation is -210° or more negative, the next recrystallization may be omitted and the levopimaric acid generated directly.

9. The maximum observed rotation for the 2-amino-2-methyl-1-propanol salt of levopimaric acid is $[\alpha]^{24D} -218^\circ$.³ Methanol and ethanol solutions give the same specific rotations, but methanol is the preferred solvent because the time required to effect solution in ethanol is longer. If pure levopimaric acid, m.p. $151-153^\circ$, $[\alpha]^{24D} -276^\circ$ is desired, the salt with -210° rotation should be dissolved in 8 parts of boiling methanol, the solution concentrated to the point of incipient crystallization, cooled, and filtered. The yield in this recrystallization is about 70%.

10. The submitters find phosphoric acid more convenient than boric acid³ or acetic acid.⁴ Acid isomerization to abietic acid^{3, 5} did not occur under the conditions used here.

11. After an induction period of approximately 1 week, the amine salt begins to be oxidized by air and the salt should be converted to levopimaric acid as soon as possible after it has been isolated.

12. The checkers found that their material with $[\alpha]^{25D} -260^\circ$ had a melting point at $125-150^\circ$. The melting point is very sensitive to impurities, and a few percent of impurities can lower it drastically.

13. The yields obtained using this procedure can vary with the source of the oleoresin; the submitters report a yield of 29-34% of levopimaric acid.

14. Using slash pine (*Pinus ellioti*) oleoresin containing ap-

proximately 16% of levopimaric acid,^{6, 7} the submitters found yields consistently less than their reported 29-34%. Pine "scrape," a material which crystallizes on the surface of the pine tree, has been used in a similar process⁴ but gives highly variable yields and, owing to interference by oxidation products, may fail to give the desired material. To avoid the deleterious effects of oxidized materials, the use of fresh oleoresin is recommended.

3. Methods of Preparation

The described process of isolating levopimaric acid is based on the method of Summers, Lloyd, and Hedrick.⁸ The procedure, a modification of the process devised by Harris and Sanderson³ and Loeblich, Baldwin, O'Connor, and Lawrence,⁴ is more convenient and gives improved yields.

4. Merits of the Preparation

In pine oleoresin, many resin acids occur. This procedure illustrates how, by the use of a specific amine, it is possible to get a specific precipitation of one resin acid from a mixture of acids.

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3-METHYLPENTANE-2,4-DIONE¹

CORRECTION

It has been reported by A. M. Roe and J. B. Harbride² that this procedure yields a product containing 20–25% of 3,3-dimethylpentane-2,4-dione as shown by gas chromatography. The amount of the dialkylation product is said to be reduced to 5–10% when the reflux period is shortened from 20 to 4.5 hours. The impurity is not readily removed but does not interfere with the preparation of 2,3,4,5-tetramethylpyrrole.³

The same authors report that the work-up of the reaction may be improved by adding 250 ml. of petroleum ether (b.p. 40–60°) to the cold reaction mixture before filtering, and washing the solids with a 1:1 mixture of acetone and petroleum ether. With this change it is not necessary to decant the product from the precipitated potassium iodide as recommended in Note 3.

1. *Org. Syntheses*, **42**, 75 (1962).

2. Private communication.

3. *Org. Syntheses*, **42**, 92 (1962).

N-MONO- AND N,N-DISUBSTITUTED
UREAS AND THIOUREAS

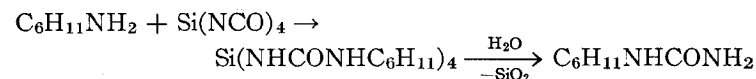
Submitted by ROY G. NEVILLE¹ and JOHN J. MCGEE²

Checked by WILLIAM E. PARHAM and J. KENT RINEHART

METHOD I

CYCLOHEXYLUREA

(Urea, cyclohexyl-)

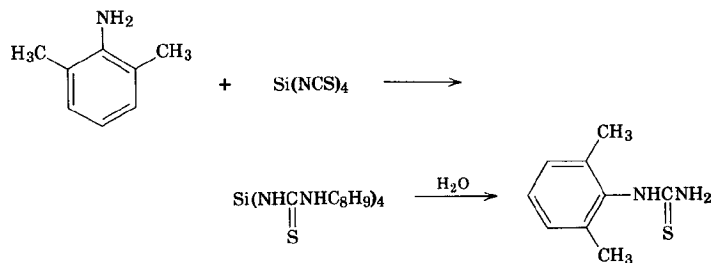


A solution of cyclohexylamine (39.7 g., 0.4 mole) (Note 1) in 100 ml. of anhydrous benzene (Note 2) is added slowly to a stirred solution (Note 3) of silicon tetraisocyanate (19.6 g., 0.1 mole) (Note 4) in 150 ml. of anhydrous benzene contained in a 1-l. round-bottomed flask. After the exothermic reaction has subsided, the mixture is heated at the reflux temperature for 30 minutes; the benzene is then removed using a rotary evaporator. Dilute isopropyl alcohol (200 ml.) (Note 5) is added to the residue, and the resulting mixture is heated at the reflux temperature for 30 minutes. The hot mixture is filtered through a 0.5-in. layer of Celite® contained in a coarse-grade sintered-glass funnel (Note 6). The gelatinous silica is washed with two 75-ml. portions of acetone and is then pressed and drained. The combined filtrates are evaporated to dryness on a steam bath (Note 7). The crude cyclohexylurea (m.p. 185–191°, 55.0 g., 97% yield) is recrystallized from 220 ml. of isopropyl alcohol (Note 8) to give 37 g. (65%) of product, m.p. 192–193°. Concentration of the mother liquor affords about 9 g. (16%) of additional product which is less pure (m.p. 189–192°) (Note 9).

METHOD II

2,6-DIMETHYLPHENYLTHIOUREA

[Urea, 1-(2,6-dimethylphenyl)-2-thio-]



Silicon tetraisothiocyanate (26.0 g., 0.10 mole) (Note 10) is finely ground under 100 ml. of anhydrous benzene, and the mixture is quickly transferred to a 1-l. round-bottomed flask. The mortar and pestle are washed with two 25-ml. portions of anhydrous benzene, and the washings are added to the flask. A solution of 2,6-dimethylaniline (48.5 g., 0.4 mole) (Note 1) in 100 ml. of anhydrous benzene is added to the well-stirred mixture. The reaction is mildly exothermic. The mixture is heated at the reflux temperature for 30 minutes, and the benzene is then removed using a rotary evaporator. Dilute isopropyl alcohol (200 ml.) (Note 5) is added to the residue, and the resulting mixture is heated at the reflux temperature for 30 minutes. The mixture is then processed in exactly the same manner as described above for the preparation of cyclohexylurea. The crude 2,6-dimethylphenylthiourea (m.p. 193–197°, 71.3 g., 99% yield) is recrystallized from 280 ml. of isopropyl alcohol (Note 8) to give 50 g. (72%) of product, m.p. 201–202°. Concentration of the mother liquor affords 11 g. (15%) of less pure product, m.p. 197–199° (Note 11).

2. Notes

1. Cyclohexylamine and 2,6-dimethylaniline were obtained from Eastman Organic Chemicals and were redistilled prior to use.

2. Benzene was dried over sodium wire.

3. The mixture becomes viscous; however, a good magnetic stirrer is adequate. The checkers found it convenient to decrease the viscosity of the mixture by increasing the volume of benzene from 100 ml. to 150–300 ml.

4. Silicon tetraisocyanate is prepared from silicon tetrachloride and silver cyanate or lead cyanate.^{3, 4}

5. Dilute isopropyl alcohol is prepared by mixing the alcohol (180 ml.) with water (20 ml.). The use of more than about 10% water in the alcohol results in an intractable mass of gelatinous silica from which it is very difficult to separate a good yield of the urea.

6. As gelatinous silica clogs the filter when too strong a suction is applied, it is best to carry out the filtration using very gentle suction. Only when almost all the liquid has passed through the filter is strong suction applied. The checkers used Hyflo Supercel® as the filter aid, and a 600-ml. coarse-grade sintered-glass funnel.

7. An open dish or a rotary evaporator is satisfactory.

8. Isopropyl alcohol is a good solvent to employ for recrystallizing most ureas; however, occasionally a mixture of alcohol and benzene or pure benzene is superior.

9. This material is of sufficient purity for most purposes. If a purer product is required, the first crop of the cyclohexylurea (37 g.) is recrystallized from 135 ml. of isopropyl alcohol to yield 23 g. of product, m.p. 195.5–196.0°

10. Silicon tetraisothiocyanate is prepared from silicon tetrachloride and silver thiocyanate^{5, 6} or, preferably, ammonium thiocyanate.^{6, 7} The silicon tetraisothiocyanate used by the checkers was slightly yellow; however, this did not affect the yield of product.

11. This material is of sufficient purity for most purposes. If purer material is required, the first crop of 2,6-dimethylphenylthiourea (50 g.) is recrystallized from 250 ml. of isopropyl alcohol to yield 41 g. of product, m.p. 203.5–204.0°.

3. Methods of Preparation

Cyclohexylurea has been prepared by the reaction of cyclohexyl isocyanate with gaseous ammonia⁸ or ammonium hydroxide,⁹ by thermal decomposition of cyclohexyl allophanamide,¹⁰ by treating cyclohexylamine hydrochloride with an aqueous solution of potassium cyanate,¹¹ by heating nitrosomethylurea with cyclohexylamine,¹² and by heating an ethanolic solution of cyclohexylamine and 3,5-dimethyl-1-carbamylpyrazole.¹³

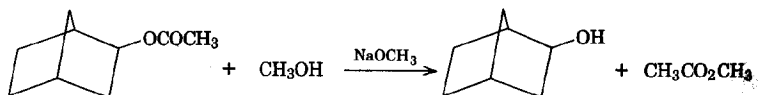
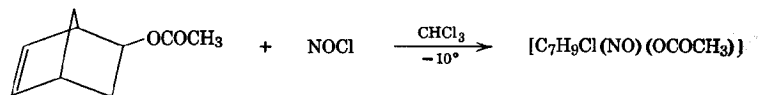
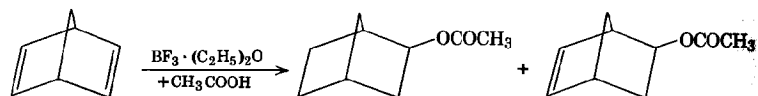
2,6-Dimethylphenylthiourea has been synthesized by allowing 2,6-dimethylaniline hydrochloride to react with ammonium thiocyanate.¹⁴

4. Merits of the Preparation

These procedures are generally applicable to aliphatic, alicyclic, aralkyl, aromatic, and heterocyclic primary or secondary amines. The reactions fail or give poor yields with sterically hindered amines such as 2-trifluoromethylaniline, 2,6-dibromoaniline, and diphenylamine. In general, however, excellent (95–100%) yields of N-mono- or N,N-disubstituted ureas or thioureas can be obtained by employing these versatile reactions which are, in most cases, superior to and supplement the methods conventionally employed for the synthesis of ureas and thioureas.¹⁵ Because of the rapidity, ease, and excellent yields of these reactions, silicon tetrakisocyanate and tetraisothiocyanate (both of which are readily prepared^{4, 6}) are likely to become standard reagents for the preparation of N-mono- and N,N-disubstituted ureas and thioureas. The submitters have employed these reagents to prepare large-scale (0.4M) amounts of the following compounds (yields in parentheses): benzylurea, m.p. 148° (96%);^{16a} phenylurea, m.p. 147° (95%);^{16b} *t*-butylurea, m.p. 182° (95%);¹⁷ N-(2-benzothiazolyl)urea, m.p. >350° (95%);^{18, 19} dibenzylthiourea, m.p. 140° (95%);^{16c} *t*-butylthiourea, m.p. 168° (98%).^{16d} In addition, the scope and limitation of the reactions of silicon tetrakisocyanate and tetraisothiocyanate have been investigated with more than fifty alkyl, aralkyl, aromatic, and heterocyclic primary and secondary amines.^{20, 21}

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NORTRICYCLANOL

(Tricyclo[2.2.1.0^{2,6}]heptan-3-ol)

Submitted by J. MEINWALD, J. CRANDALL, and W. E. HYMANS¹
 Checked by J. R. ROLAND and B. C. MCKUSICK

1. Procedure

A. Nortricyclyl acetate. A mixture of 156 g. (1.70 moles) of bicyclo[2.2.1]hepta-2,5-diene (Note 1), 105 g. (100 ml., 1.75 moles) of glacial acetic acid, and 3 ml. of boron trifluoride etherate (Note 2) is placed in a 500-ml. flask attached to a condenser equipped with a drying tube. The mixture is heated on a steam bath for 6 hours, cooled to room temperature, and diluted with 250 ml. of ether. The ethereal solution is washed successively with two 50-ml. portions of 3*N* ammonia and 50 ml. of water and dried over magnesium sulfate. The ether is removed by distillation through a short column of glass helices, and the dark

residue is distilled under reduced pressure to give about 200 g. of a mixture of nortricyclyl acetate and bicyclo[2.2.1]hepta-5-en-2-yl acetate as a colorless liquid, b.p. 85–95° (15 mm.) (Note 3).

The acetate mixture is dissolved in 500 ml. of chloroform (analytical reagent grade) in a 2-l. Erlenmeyer flask equipped with a thermometer and a gas-inlet tube and located in a good hood. *Caution! All operations using nitrosyl chloride should be performed in a good hood.* The solution is cooled to –10° in an ice-salt bath, and nitrosyl chloride (Note 4) is bubbled into the solution with swirling at –10° ± 3° until the color of the solution changes through bright green to a brownish green that indicates excess nitrosyl chloride. A white precipitate begins to form at this point. There is added 500 ml. of 30–60° petroleum ether, and the mixture is cooled at –10° ± 3° for an additional 15 minutes. The precipitated nitrosyl chloride adduct (Note 5) is collected by suction filtration (*Caution! Hood*). The filtrate is washed successively with two 200-ml. portions of saturated sodium carbonate solution and 500 ml. of saturated sodium chloride and dried over magnesium sulfate. The solvent is removed through a short column of glass helices, and the dark residue is distilled under reduced pressure (*Caution! Note 6*) to give 132–167 g. (52–66%) of nortricyclyl acetate as a faintly green liquid, b.p. 83–85° (13 mm.), *n*_D²⁵ 1.4673–1.4681 (Note 7).

B. Nortricyclanol. The nortricyclyl acetate obtained above is added to a solution of 0.5 g. of sodium in 500 ml. of anhydrous methanol (analytical grade reagent). The solution is heated on a steam bath, and the methanol is slowly distilled through a short column packed with glass helices (Note 8). The residue is cooled, diluted with 250 ml. of 30–60° petroleum ether, and the solution is washed with two 50-ml. portions of water and dried over magnesium sulfate. The solvent is removed by distillation through a short column packed with glass helices, finally at 25° and water-pump pressure. The crude product, which solidifies on cooling, is sublimed at 80° (2 mm.) to yield 84–107 g. (45–57% based on bicycloheptadiene; Note 9) of nortricyclanol, m.p. 108–110°. It is pure enough for most purposes. A slightly purer product is obtained by resublimation (Note 10).

2. Notes

1. Bicycloheptadiene supplied by Shell Chemical Corporation can usually be used without purification. If the material is cloudy or contains a precipitate, it should be distilled before being used.
2. The purified grade of Eastman Organic Chemicals is satisfactory. After the procedure had been checked, the submitters found that the use of only 1 ml. of this reagent gave the specified yield more consistently.
3. The exact proportion of unsaturated acetate varies slightly but is typically 10–15% as determined by vapor-phase chromatography.
4. Nitrosyl chloride from the Matheson Company is satisfactory.
5. The adduct may be recrystallized from chloroform to give a white crystalline product, m.p. 152–153°.
6. The hot residue decomposes vigorously with the evolution of irritating gases when opened to the atmosphere. Consequently, the distillation flask should be cooled to room temperature before breaking the vacuum.
7. Vapor-phase chromatographic analysis of this product showed less than 1% of isomeric material.
8. The checkers used a 1.3-cm. x 25-cm. column of helices and removed the solvent over a period of about 5 hours.
9. The yield of nortricyclanol from nortricyclyl acetate is 82–95%.
10. Vapor-phase chromatography shows no detectable impurities under conditions where <1% of isomeric material would be easily visible. A melting point of 108–109° has been reported.²

3. Methods of Preparation

The addition of carboxylic acids to bicyclo[2.2.1]hepta-2,5-diene has been described by several authors;³ the method described here is a modification of these procedures. Nortricyclanol has been prepared by the hydration of bicyclo[2.2.1]hepta-2,5-diene⁴ and the solvolysis of nortricyclyl² and bicyclo[2.2.1]hept-2-en-5-yl⁵ halides, as well as by the saponification^{3a, 6} and

transesterification^{3a} of the corresponding esters. The described conversion of the acetate to the alcohol is patterned after a similar procedure of Hall.^{3c}

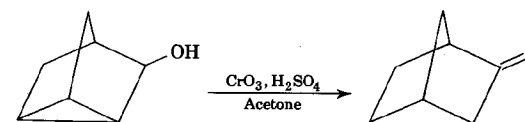
4. Merits of the Preparation

The present preparation affords high-purity nortricyclanol in good yield without the necessity of tedious purification. It illustrates a convenient way to convert olefins to alcohols and to remove olefinic impurities from alcohols. Nortricyclanol is of current interest in studies of highly strained ring systems. It is readily oxidized to nortricyclanone.⁷

1. Department of Chemistry, Cornell University, Ithaca, New York.
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NORTRICYCLANONE

(Tricyclo[2.2.1.0^{2,6}]heptan-3-one)



Submitted by J. MEINWALD, J. CRANDALL, and W. E. HYMANS¹
 Checked by J. R. ROLAND and B. C. MCKUSICK

1. Procedure

The oxidation reagent is prepared by dissolving 70 g. (0.70 mole) of chromium trioxide in 100 ml. of water in a 500-ml.

beaker. The beaker is immersed in an ice bath, and 112 g. (61 ml., 1.10 moles) of concentrated (18*M*) sulfuric acid followed by 200 ml. of water is added cautiously with manual stirring. The solution is cooled to 0–5°.

A solution of 110 g. (1.00 mole) of nortricyclanol (Note 1) in 600 ml. of acetone (analytical reagent grade) is cooled to 0–5° in a 2-l. three-necked flask immersed in an ice bath and equipped with an efficient mechanical stirrer, a thermometer, and a dropping funnel with a pressure-equalizing arm. The cooled oxidation reagent prepared above is poured into the dropping funnel, and the reagent is added with vigorous stirring, at a rate to maintain the temperature of the reaction mixture at about 20°. The stirring is continued for 3 hours after the addition is completed.

Sodium bisulfite is added in small portions until the brown color of chromic acid is gone from the upper layer of the two-phase mixture. The top layer is decanted, and the dense, green, lower layer is extracted with 200 ml. of 30–60° petroleum ether. Combination of this extract with the original upper layer causes a separation into two phases. The lower phase is drawn off and added to the original lower phase, which is then extracted with three 200-ml. portions of 30–60° petroleum ether (Note 2). The extracts are combined, washed successively with two 50-ml. portions of saturated sodium chloride, two 50-ml. portions of saturated sodium bicarbonate solution, and 50 ml. of saturated sodium chloride solution, and dried over magnesium sulfate. The solvent is removed by distillation through a short column containing glass helices, and the residue is distilled under reduced pressure to give 85–95 g. (79–88%) of nortricyclanone, b.p. 103–105° (77 mm.), n_D^{26} 1.4873 (Notes 3 and 4).

2. Notes

1. The preparation of nortricyclanol is described in this volume, p. 74. The crude, unsublimed nortricyclanol is a satisfactory starting material.

2. Sufficient time between extraction and separation of layers must be allowed, for the organic layer separates slowly from the thick aqueous phase.

3. The product was shown to contain <1% of the starting material and no other detectable impurity by vapor-phase chromatographic analysis.

4. The reported² properties of this material are b.p. 78–79° (24 mm.), n_D^{25} 1.4878.

3. Methods of Preparation

Nortricyclanone has been prepared by oxidation of nortricyclanol using chromic acid in acetic acid^{2, 3} and using a modified Oppenauer reaction.⁴ The present procedure is based on the Jones modification⁵ of chromic acid oxidations.

4. Merits of the Preparation

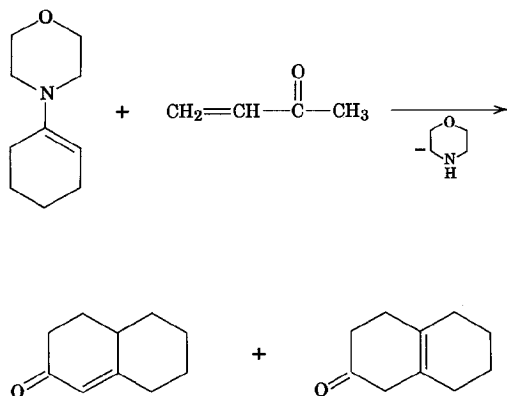
This preparation illustrates a general and convenient way of oxidizing secondary alcohols to ketones. The novel feature of the reaction is represented by acetone solvent which affects markedly the properties of the oxidizing agent. The reaction is very rapid (if not instantaneous), and the yields are high, the reagent rarely attacking unsaturated centers. The procedure is applicable to acetylenic carbinols, allyl and other unsaturated alcohols, and saturated carbinols. The main limitation is the low solvent power of acetone.

The preparation illustrates the utility of the reaction in preparing the highly strained and reactive nortricyclanone, a compound of current interest in studies of strained ring systems.

1. Department of Chemistry, Cornell University, Ithaca, New York.
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$\Delta^{1(9)}$ -OCTALONE-2

[2(3H)-Naphthalenone, 4,4a,5,6,7,8-hexahydro-]



Submitted by ROBERT L. AUGUSTINE and JOSEPH A. CAPUTO¹
 Checked by WILLIAM G. DAUBEN and JEFFREY N. LABOVITZ

1. Procedure

A. $\Delta^{1(9)}$ -Octalone-2 and $\Delta^{9(10)}$ -octalone-2. In a 2-l., three-necked, round-bottomed flask equipped with a sealed stirrer, a condenser, and a dropping funnel is placed a solution of 102 g. (0.61 mole) of 1-morpholino-1-cyclohexene² (Note 1) in 600 ml. of purified dioxane (Notes 2 and 3). To this stirred solution is added 45 g. (0.64 mole) of freshly distilled methyl vinyl ketone at such a rate that the addition requires approximately 1 hour. The resulting solution is heated under reflux for 4 hours, after which time 750 ml. of water is added, and the heating under reflux is continued for an additional 10–12 hours. The solution is cooled to room temperature and poured into 1 l. of water. The resulting mixture is extracted four times with 500-ml. portions of ether. The combined ether extracts are washed three times with 250-ml. portions of 3*N* hydrochloric acid, twice with 100-ml. portions of a saturated aqueous sodium bicarbonate solution, once with a 250-ml. portion of water, once with a 200-ml. portion of a saturated aqueous sodium chloride solution, and

dried over anhydrous magnesium sulfate. The mixture is filtered, the ethereal filtrate evaporated, and the residual octalones distilled through a short column. The yield is 54–59 g. (59–65%) of an octalone mixture (Note 4), b.p. 75–78° (0.2 mm.), 101–103° (2 mm.).

B. $\Delta^{1(9)}$ -Octalone-2. A solution of 35 g. (0.23 mole) of the above octalone mixture in 200 ml. of 60–110° petroleum ether is cooled to –80° in an acetone-dry ice bath and kept at this temperature for 1 hour. The crystalline $\Delta^{1(9)}$ -octalone-2 is filtered by suction through a jacketed sintered-glass funnel kept at –80°. The residue is washed with 100 ml. of cold petroleum ether, removed from the funnel, and recrystallized a second time in the same way. After the second recrystallization the white crystals are removed from the funnel, allowed to melt by warming to room temperature, and distilled. The yield of purified $\Delta^{1(9)}$ -octalone-2 (Note 5), b.p. 143–145° (15 mm.), is 20–25 g. (34–46% based on starting enamine). The petroleum ether mother liquors can be distilled to yield a fraction boiling at 143–145° (15 mm.) which is enriched in $\Delta^{9(10)}$ -octalone-2.

2. Notes

1. The enamine should be utilized as soon as possible after distillation.
2. A suitably purified dioxane can be obtained by distillation of reagent grade dioxane from lithium aluminum hydride.
3. Absolute ethanol and dry benzene are also useful solvents for enamine reactions. In this instance, however, the use of these solvents results in a lower yield of octalones.
4. The octalone mixture contains 10–20% of the $\Delta^{9(10)}$ -isomer. This mixture may be used as such for many purposes.
5. The purified octalone still contains 1–3% of the $\Delta^{9(10)}$ -isomer which cannot be removed even on further crystallization.

3. Methods of Preparation

The method of preparation used here is styled after the general procedure described for the reaction of enamines with electro-

philic olefins.³ $\Delta^1(9)$ -Octalone-2 also has been prepared by condensation of 4-diethylamino-2-butanone with cyclohexanone; by condensation of 2-diethylaminomethylcyclohexanone with ethyl acetoacetate;⁴ by condensation of methyl vinyl ketone with cyclohexanone;⁵ by condensation of 4-oxo-1,1-dimethylpiperidinium salts with 2-carbethoxycyclohexanone;⁶ by the oxidation of α -decalones;⁷ and by the reduction of 6-methoxytetralin.⁸

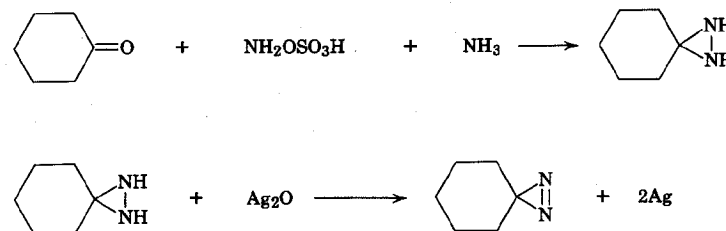
4. Merits of the Preparation

The present procedure is a general method for the preparation of monoalkylated ketones from enamines of aldehydes and ketones with electrophilic olefins.³ There are many advantages in this method of alkylation. Only monoalkylation occurs, even when such reactive species as acrylonitrile are used; and, when a cyclic ketone like 2-methylcyclohexanone is used, reaction occurs only at the lesser substituted center. In a general base-catalyzed reaction, substitution occurs on the more substituted center.

Another advantage of this method is that no catalyst is needed for the addition reaction; this means that the base-catalyzed polymerization of the electrophilic olefin (*i.e.*, α,β -unsaturated ketones, esters, etc.) is not normally a factor to contend with, as it is in the usual base-catalyzed reactions of the Michael type. It also means that the carbonyl compound is not subject to aldol condensation which often is the predominant reaction in base-catalyzed reactions. An unsaturated aldehyde can be used only in a Michael addition reaction when the enamine method is employed.

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3,3-PENTAMETHYLENEDIAZIRINE



Submitted by ERNST SCHMITZ and ROLAND OHME¹
 Checked by E. J. COREY and RICHARD GLASS

1. Procedure

A. *3,3-Pentamethylenediaziridine*. A solution of 147 g. (1.5 moles) of cyclohexanone in 400 ml. of 15*N* aqueous ammonia (6.0 moles) in a 1-l. beaker is stirred mechanically and cooled to 0° with an ice-salt mixture. Maintaining the temperature of the solution between 0° and +10°, 124 g. (1.0 mole) of 90% hydroxylamine-O-sulfonic acid (Note 1) is added in portions of about 1 g. The addition requires about 1 hour, and the mixture is stirred for another hour at 0° and allowed to stand overnight at -15° in a refrigerator. The precipitated crystalline cake is filtered and pressed tight with a glass stopper. The solid is washed with 50-ml. portions of ice-cold ether, toluene, and finally ether. There is obtained 110–115 g. of product which is 70–90% pure (Notes 2 and 3). The product is divided into two portions, each of which is boiled briefly with a 50-ml. portion of toluene; the solutions are decanted from small salt residues and cooled to 0° for 2 hours. The precipitates are filtered with suction and washed with 50 ml. of ice-cold petroleum ether. The combined yield of 3,3-pentamethylenediaziridine is 68–78 g. (61–70%), m.p. 104–107°. The purity is 96–100% (Note 4).

B. *3,3-Pentamethylenediazirine*. *Caution! See Note 5.* A solution of 34.0 g. (0.2 mole) of silver nitrate in 100 ml. of water is treated dropwise, with shaking, with 100 ml. of 2*N* sodium hydroxide. The precipitate is filtered with suction and washed

thoroughly with water, methanol, and lastly ether. A mixture of 10.0 g. (0.089 mole) of 3,3-pentamethylenediaziridine (Note 5) and 220 ml. of ether is warmed, the resulting solution cooled to room temperature, and within a 5-minute period the silver oxide prepared above is added in small portions, with shaking, to the cooled solution. During the addition the reaction mixture is cooled with tap water and then is shaken without cooling until an aliquot does not liberate iodine from an acidified iodide solution; the reaction is normally complete in 30–60 minutes. The mixture is filtered through a fluted filter, the solid residue washed with a small volume of ether, and the filtrate dried over potassium carbonate. The ether is distilled at a bath temperature of 45° through a 30-cm. Vigreux column. The last 20 ml. of the solvent is removed at a pressure of 30 mm. and a bath temperature of 10°. Using a protective shield, the residue is distilled at 33° (30 mm.) to yield 6.4–7.4 g. (65–75%) of 3,3-pentamethylenediazirine. In order to prevent decomposition of the product on storage, it is diluted with ether and kept in a refrigerator.

2. Notes

1. Hydroxylamine-O-sulfonic acid is prepared according to the method of Gösl and Meuwesen,² or of Matsuguma and Audrieth.³ The material is available from Eastman Organic Chemicals.

Analysis of this substance, just prior to use, is carried out in the following manner. A sample is dissolved in water and treated with a solution of potassium iodide in 2*N* sulfuric acid. After 5 minutes the solution is titrated with thiosulfate solution; near the end of the titration the solution is boiled to ensure completeness of iodine liberation. Instead of the 90% product, a correspondingly greater amount of the 80% product can be employed.

2. For the analysis an ethanolic solution of the 3,3-pentamethylenediaziridine is treated with a solution of potassium iodide in 2*N* sulfuric acid. It liberates two equivalents of iodine instantaneously.

3. The crude product is recrystallized without additional drying; it undergoes partial decomposition on standing.

4. If subsequent treatment is not to be performed within a

few days, it is recommended that the preparation be recrystallized a second time to obtain a stable product. Smaller amounts can be advantageously purified by vacuum sublimation.

5. It is recommended that the dehydrogenation be done with small amounts if the dehydrogenation product is to be isolated. Although decomposition was never observed with the preceding procedure, *diazirines should be handled with caution. Explosions were reported when working with 3-methyldiazirine⁴ and 3-*n*-propyldiazirine⁴ as well as when overheating pentamethylenediazirine.⁵* Most of the reactions of diazirines, especially the reaction with Grignard compounds,⁵ can be done without purification of the diazirine.

3. Methods of Preparation

Diazirines have been prepared by dehydrogenation of diaziridines with mercuric oxide,⁶ silver oxide,⁵ or dichromate-sulfuric acid.⁴ The present procedure corresponds to that of Schmitz and Ohme.⁵ The procedure for the preparation of the 3,3-pentamethylenediaziridine has been reported by H. J. Abendroth.⁸

4. Merits of the Preparation

Diazirines are the cyclic isomers of the aliphatic diazo compounds. Both the diaziridines and the diazirines are starting materials for the synthesis of alkyl hydrazines. 3,3-Pentamethylenediaziridine can be hydrolyzed quantitatively to hydrazine. Methylamine⁹ may be substituted for ammonia in the procedure resulting in 1-methyl-3,3-pentamethylenediaziridine (m.p. 35–36°, yield 62% of theoretical) and then methyl hydrazine. Use of ethylenediamine leads to ethylene bis-hydrazine⁷ via a bifunctional diaziridine (m.p. 143–144°, yield 48% of theoretical). Ammonia can also be replaced by *n*-propylamine⁸ or cyclohexylamine⁷; cyclohexanone by acetone.

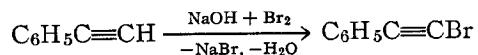
3,3-Pentamethylenediazirine and other diazirines easily add Grignard reagents to the N—N double bond. The reaction leads to N-alkyl diaziridines which can be hydrolyzed to alkyl hydrazines. Cyclohexylhydrazine (85% yield), *n*-propylhydrazine (88%), isopropylhydrazine (95%), and benzylhydrazine were

prepared from 3,3-pentamethylenediazirine and the corresponding Grignard reagent.¹⁰

1. Institute for Organic Chemistry of the German Academy of Sciences, Berlin-Adlershof, East Germany.
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PHENYLBROMOETHYNE

(Benzene, bromoethynyl)



Submitted by SIDNEY I. MILLER, GENE R. ZIEGLER, and R. WIELESECK¹
 Checked by WILLIAM E. PARHAM and JAMES N. WEMPLE

1. Procedure

To a 2-l. bottle equipped with a rubber stopper and immersed in a mixture of ice and water (slush) there is added a cold (about 0°) solution containing 300 g. (7.5 moles) of sodium hydroxide (Note 1) and 800 ml. of water. The mixture is swirled or stirred while 160 g. (2 moles) of bromine is added. Phenylacetylene (84 g., 0.82 mole) (Note 2) is then added to the yellow solution, and the resulting mixture is stoppered and shaken. The rubber stopper is wired down, the bottle is covered with opaque cloth or paper, and the bottle is then placed in a mechanical shaker for 60 hours at room temperature (Note 3).

The crude oil is then separated from the aqueous phase, dried with calcium chloride (Note 4), and fractionated (Note 5) at reduced pressure under nitrogen (*Caution!* Note 6). The distillation receiver should be cooled in an ice-salt or dry ice-acetone mixture. After a small fore-run of phenylacetylene, there is

obtained 109–124 g. (73–83% yield) of water-white phenylbromoethyne, b.p. 40–41° (0.1 mm.), n_D^{25} 1.6075 (Note 7).

2. Notes

1. Practical grade sodium hydroxide and bromine were used.
2. Commercially available phenylacetylene can be used. The checkers used material as obtained from Columbia Organic Chemicals Co., Inc.
3. Vigorous shaking is essential. An ordinary motor-driven stirrer proved to be inadequate. Phenylbromoethyne gradually darkens when exposed to light or air. The product is best stored under nitrogen in a refrigerator and should be distilled within a few days of its preparation.
4. The checkers observed that the calcium chloride absorbs appreciable quantities of product. The crude oil was dissolved in peroxide-free ether (about 300 ml.) prior to drying with calcium chloride, or the calcium chloride was extracted with several 50-ml. portions of dry ether after use. The ethereal extracts were concentrated under nitrogen and added to the product before distillation.
5. The checkers distilled the product from a flask equipped with a Claisen head but no column.
6. No air should be allowed to come in contact with the hot pot liquid during the distillation, for an exothermic reaction may occur; at best this may fill the apparatus with tarry material and the room with noxious fumes; at worst, pressure built up may destroy all or part of the apparatus. As a precaution, this distillation should be carried out behind a safety shield.
7. The checkers observed that the refractive index of a sample stored for 5 days in the refrigerator in a stoppered tube wrapped in aluminum foil and cloth changed from n_D^{25} 1.6074 to n_D^{25} 1.6082.

3. Methods of Preparation

Phenylbromoethyne has been prepared by base-catalyzed dehydrobromination of 1,1- or 1,2-dibromostyrene;² by the thermal

decomposition of silver 1,2-dibromocinnamate;² from phenylethynylmagnesium Grignard reagent and bromine;^{3,4} cyanogen bromide,⁵ or benzenesulfonic anhydride;⁶ from phenylethynylsodium and cyanogen bromide⁴ or *p*-toluenesulfonylbromide⁷; from phenylethynylsilver and bromine in pyridine;⁸ and from phenylethynyllithium and N-bromoimides.⁹ The present method is a modification of one in which the hypobromite-phenylacetylene mixture is warmed for 1.5 hours in the presence of an emulsifying agent, 1% potassium stearate¹⁰ or soap,¹¹ to give 88% yield of product.

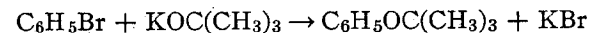
4. Merits of the Preparation

The hypohalite route to 1-chloro-, 1-bromo-, or 1-iodoalkynes is both general and convenient. The purity of the reagents does not appear to be critical.

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PHENYL *t*-BUTYL ETHER

(Ether, *t*-butyl phenyl)



Submitted by MELVILLE R. V. SAHYUN and DONALD J. CRAM¹
 Checked by WILLIAM G. DAUBEN and DAVID J. ELLIS

1. Procedure

In a loosely stoppered 1-l. round-bottomed flask are placed 37.5 g. (48 ml.) of *t*-butyl alcohol, 150 ml. of dimethyl sulfoxide (Note 1), and a Teflon®-coated magnetic stirring bar. The solution is heated in an oil bath which is placed on a combination magnetic stirrer-hotplate. When the temperature of the mixture reaches 125–130°, 75 g. (0.67 mole) of alcohol-free potassium *t*-butoxide (Notes 2 and 3) is added, the stopper is replaced loosely, and the mixture is stirred. When all the potassium *t*-butoxide is in solution, the stopper is removed, 25 g. (0.159 mole, 17 ml.) of bromobenzene is added in one portion to the hot solution, and an air condenser fitted with a drying tube is *rapidly* placed on the flask. The solution immediately turns dark brown, and an extremely vigorous, exothermic reaction occurs. After 1 minute the reaction mixture is poured into 500 ml. of water. The aqueous solution is saturated with sodium chloride and extracted with four 200-ml. portions of ether (Note 4). The ether extract is washed with three 100-ml. portions of water and dried over anhydrous potassium carbonate. The ether is distilled at atmospheric pressure on a steam bath to leave 17–18 g. of crude phenyl *t*-butyl ether (Note 5). The brown oil is distilled to yield 10–11 g. (42–46%) of pure phenyl *t*-butyl ether, b.p. 45–46° (2 mm.), m.p. –17 to –16°, n_D^{25} 1.4860–1.4890 (Note 6). The ether may be hydrolyzed readily to phenol (Note 7).

2. Notes

1. "Baker Analyzed" dimethylsulfoxide, which is freshly opened and dry to Karl Fischer reagent, is used without further purification.

2. Commercial potassium *t*-butoxide is used directly as obtained from the Mine Safety Appliance Research Corp., Callery, Pennsylvania.

3. This amount of potassium *t*-butoxide is not soluble in the dimethylsulfoxide at a lower temperature. An excess of base over *t*-butyl alcohol is necessary to the reaction, and a high concentration of *t*-butyl alcohol (3.3*M*) considerably improves the yield of product desired.

4. The aqueous residue from the extraction can be acidified and extracted to yield phenol which is purified by chromatography on a silica gel column, with an eluant solution composed of 95% pentane and 5% ether by volume. The purified phenol weighs 4.3 g. (29% of the theoretical amount) and is obtained as long needles.

5. The crude material also contains some polymeric material and traces of solvent. Gas chromatography indicates that the phenyl *t*-butyl ether is 60–70% pure at this point.

6. The checkers found their product to contain 0.5–1.0% bromobenzene. Careful redistillation is required to free the product of this impurity.

7. Phenyl *t*-butyl ether is swirled with 6*N* hydrochloric acid until solution is completed. The solution is then saturated with sodium chloride and extracted with ether to yield phenol, identifiable as the tribromide.

3. Methods of Preparation

The procedure described here is based on a method outlined by Cram, Rickborn, and Knox.² The method is not a general one for the preparation of a substituted phenyl *t*-butyl ether because an aryne intermediate is involved. It appears that aryl fluorides undergo direct substitution to yield unrearranged aryl

t-butyl ethers. Alternative methods for preparation of these ethers are listed in an early preparation of the compound.³

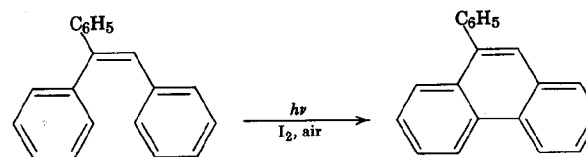
4. Merits of the Preparation

This reaction sequence illustrates how the rates of many base-catalyzed reactions can be enhanced greatly by substitution of dimethylsulfoxide for the usual hydroxylic solvents.⁴ Other examples of the enhanced reactivity of anions in dimethylsulfoxide are found in Wolff-Kishner reductions and Cope elimination reactions.⁵ The present reaction illustrates the generation of an aryne intermediate from bromobenzene.⁵

1. Department of Chemistry, University of California, Los Angeles 24, California.
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9-PHENYLPHENANTHRENE

(Phenanthrene, 9-phenyl-)



Submitted by FRANK B. MALLORY and CLELIA S. WOOD¹
Checked by WILLIAM G. DAUBEN and DONALD N. BRATTESANI

1. Procedure

A solution of 2.56 g. (0.01 mole) of triphenylethylene² (Note 1) and 0.127 g. (0.5 mmole) of iodine in 1 l. of cyclohexane (Note 2) is placed in a 1.5-l. beaker and stirred magnetically (Note 3). A Hanovia water-cooled 19433 Vycor immersion well fitted with a

200-watt 654A-36 mercury lamp (Notes 4 and 5) is inserted into the beaker, and the lamp is started (Note 6). The irradiation is continued for about 3 hours (Note 7).

The reaction mixture is transferred to a 2-l. round-bottomed flask, and the solvent is evaporated under reduced pressure (Note 8). The residue is dissolved in 50 ml. of warm cyclohexane (Note 2), and the solution (Note 9) is poured onto a column of alumina (Note 10) 1.8 cm. in diameter and 6–7 cm. in length. The round-bottomed flask is rinsed with three 10-ml. portions of cyclohexane, and the rinsings are poured onto the column. The column is eluted with additional cyclohexane (about 100 ml.) until no appreciable amount of 9-phenylphenanthrene is obtained in the eluate. The elution of any yellow material from the column should be avoided. The total eluate is evaporated to dryness under reduced pressure (Note 8), and the residue is recrystallized from 40–45 ml. of 95% ethanol to give 1.65–1.90 g. (65–75%) of 9-phenylphenanthrene, m.p. 103.5–104.5° (Notes 11, 12, and 13).

2. Notes

1. The triphenylethylene used by the submitters had been recrystallized from absolute ethanol, and the material melted at 68.0–68.6°.

2. Eastman Organic Chemicals practical grade cyclohexane is distilled before use.

3. A 4-cm. Teflon®-coated stirring bar gives sufficiently effective stirring.

4. This unit is sold as a Hanovia Laboratory Photochemical Reactor by the Hanovia Lamp Division, Engelhardt Industries, Inc., 100 Chestnut Street, Newark 5, New Jersey.

5. A relatively inexpensive light source and probe can be made as described below and used in place of the Hanovia unit. A 100-watt General Electric H100A4/T or H100A38-4 mercury lamp, available from the Lamp Department, General Electric Co., Nela Park, Cleveland 12, Ohio, is modified by cutting away the outer glass envelope and by detaching the inner quartz bulb from the screw base on which it is mounted. The two electrical

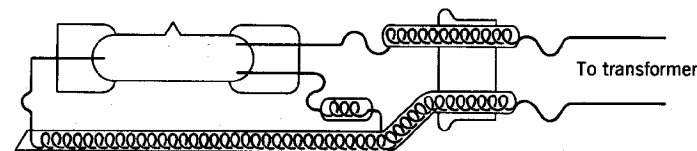


FIG. 2

leads from the lamp are then connected, as shown in Fig. 2, by means of insulated wire to a suitable power supply such as a General Electric 9T64Y-3518 or 9T64Y-1019 transformer. The modified mercury lamp is then inserted in a 17-mm. I.D. quartz tube which is about 30 cm. long and is sealed on one end. This tube is made from Clear Fused Quartz tubing available from the Lamp Glass Department, General Electric Co., Nela Park, Cleveland 12, Ohio.

Irradiations with this type of light source are carried out using a 1-l. Erlenmeyer flask as the reaction vessel instead of a 1.5-l. beaker. The flask is placed in a cold-water bath that is supported on a magnetic stirrer. The bath can be made from a 10-qt. polyethylene bucket with a $\frac{3}{4}$ -in. hole bored about 1 in. from the top of the bucket and a piece of rubber tubing with a $\frac{5}{8}$ -in. bore and $\frac{1}{8}$ -in. wall inserted as a drain. A stream of 24° tap water run into the bucket at a flow rate of 5 l. per min. maintains the temperature of the reaction mixture below 33°.

6. Unfiltered light from mercury lamps is damaging to the eyes; suitable precautions, such as wearing appropriate glasses and surrounding the reaction vessel with aluminum foil, should be taken.

7. The irradiation time required depends on the type of light source used and can be determined by following the progress of the reaction by infrared spectroscopy. A 10-ml. aliquot is withdrawn from the reaction mixture and evaporated to dryness under reduced pressure; the residue is dissolved in 0.5 ml. of carbon tetrachloride, and the spectrum is obtained using 0.1-mm. sodium chloride cells. A new peak appears at 899 cm^{-1} , and the ratio of the absorbance of the peak at 703 cm^{-1} to that of the peak at 727 cm^{-1} continuously decreases during the course of the reaction. Using these spectral criteria, the submitters judged the

reaction to be complete after 4 hours of irradiation with the lamp described in Note 5; however, the recrystallized products from 4-hour reactions melted about 0.4° lower than those from 5-hour reactions. The submitters found that varying the irradiation time from 4 hours to 8 hours had no significant effect on the yield of 9-phenylphenanthrene. The extent of the reaction can also be monitored by gas-liquid chromatography.

8. It is convenient to use a rotary evaporator and a water aspirator for this operation.

9. This solution may be purple in color owing to incomplete removal of iodine during the reduced-pressure evaporation.

10. The submitters used Merck 71707 aluminum oxide. The checkers used Woelm neutral alumina, Activity I.

11. A sample of 9-phenylphenanthrene that had been exhaustively purified by zone refining and by recrystallization melted at $104.1\text{--}104.7^{\circ}$. The melting point has been reported as $104\text{--}105^{\circ}$ ³⁻⁵ and as $105\text{--}106^{\circ}$.^{6, 7}

12. Reactions carried out at higher concentrations or on larger scales give slightly lower yields of less pure material. To obtain larger amounts of the product, the submitters recommend irradiating in batches on the scale specified in the procedure and combining the reaction mixtures prior to the chromatographic purification.

13. Using the apparatus described in Note 5, the submitters obtained 2.08–2.17 g. (82–85%) of 9-phenylphenanthrene.

3. Methods of Preparation

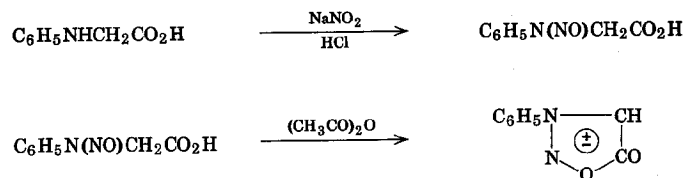
This preparation is based on a procedure published by the submitters.^{8, 9} 9-Phenylphenanthrene has been prepared previously by the reaction of phenyllithium with 9-chlorophenanthrene,¹⁰ by the high-temperature dehydrogenation with palladium on charcoal of the Diels-Alder dimer of 1-phenyl-1,3-butadiene,¹¹ and by the acid-catalyzed cyclization of the alcohol formed from the reaction of 2-biphenylmagnesium iodide and 2-phenoxyacetophenone.³

4. Merits of the Preparation

This preparation illustrates a reasonably general method for obtaining 1-, 3-, or 9-substituted phenanthrenes in good yields from the photocyclization of the corresponding *o*-, *p*-, or α -substituted stilbenes.^{8, 9} The submitters have obtained satisfactory results with bromo, chloro, fluoro, methoxy, methyl, phenyl, trifluoromethyl, and carboxyl substituents. α -Styrylnaphthalene gives chrysene, β -styrylnaphthalene gives benzo[*c*]phenanthrene, and 1,2-di- α -naphthylethylene gives picene.

The photocyclization has been found not to occur with stilbenes substituted with acetyl, dimethylamino, or nitro groups. Iodo substituents are replaced by hydrogen by photolysis in cyclohexane solution.^{9, 12} *m*-Substituted stilbenes give mixtures of 2- and 4-substituted phenanthrenes which generally are difficult to separate.

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3-PHENYLSYDNONE**(N-Phenylsydnone)**

Submitted by CHARLES J. THOMAN and DENYS J. VOADEN¹
 Checked by WILLIAM E. PARHAM and EDWARD A. WALTERS

1. Procedure

A. *N-Nitroso-N-phenylglycine*. One hundred grams (0.66 mole) of N-phenylglycine (Note 1) is suspended in 1.2 l. of water contained in a 3-l. beaker placed in an ice-salt bath and stirred until the temperature has dropped below 0°. A solution of 50 g. (0.72 mole) of sodium nitrite in 300 ml. of water is added dropwise over a period of 40 minutes at such a rate that the temperature never exceeds 0°. The red, almost clear solution (Note 2) is filtered as quickly as possible with suction, after which 3 g. of Norit® is added and allowed to stir with the cold solution for several minutes (Note 3). The mixture is again filtered with suction. Addition of 100 ml. of concentrated hydrochloric acid to the well-stirred solution produces, after about 30 seconds, a profusion of light, fluffy crystals. The suspension is stirred for 10 minutes and is then filtered with suction and washed twice with ice-cold water. The precipitate is best dried by leaving it on the suction funnel overnight. The resulting product melts at 103–104°, weighs 96–99 g. (80–83%) (Note 4), and is off-white in color. It can be used without recrystallization.

B. *3-Phenylsydnone*. The 99 g. (0.55 mole) of N-nitroso-N-phenylglycine is dissolved in 500 ml. of acetic anhydride in a 1-l. Erlenmeyer flask fitted with a reflux condenser topped by a drying tube. The deep-red solution is heated in a boiling water bath

for 1.5 hours with magnetic stirring (Note 5) and is then allowed to cool to room temperature. The cool solution is poured slowly into 3 l. of cold water which is very well stirred (Note 6); white crystals separate almost immediately. After 5 minutes of stirring, the solid is filtered with suction, washed twice with ice-cold water, and dried on the funnel with suction overnight. The dried product is cream-colored, weighs 74–75 g. (83–84%), and melts at 136–137° (Note 7). The overall yield for the two steps is 67–70%.

2. Notes

1. Eastman Organic Chemicals practical grade material, mud-brown in color, was used without purification.

2. Often a small amount of insoluble, dark-brown material remains in suspension. Filtration of this product is most difficult, since it tends to clog the filter paper. It seems advisable to change filter papers two or three times during the filtration, if necessary. This step usually requires from 30 minutes to 1.5 hours; however, the time can be shortened appreciably by the use of Hyflo Supercel®.

3. This Norit® treatment, when combined with the preceding filtration, does much to improve the purity of the N-nitroso-N-phenylglycine; though the yield of nitroso compound thereby is lowered, the yield of the sydnone is increased correspondingly and the sydnone is much purer.

4. Earl and Mackney² report a tan product (96.8% yield) melting at 102–103°. They did not use the preliminary filtration or Norit® treatment described above.

5. The usual method (Earl and Mackney²) has been to let the solution stand at room temperature for 24 hours. Control experiments proved, however, that the procedure described above gives comparable results.³

6. On rare occasions a small amount of insoluble material may be present in the cool solution; the solution can be poured into the water through a funnel fitted with a plug of glass wool.

7. Earl and Mackney² report a very light tan product, melting at 134–135°, in 73% yield. The product can be recrystallized

from boiling water to give cream-colored needles, but this does not improve the purity of the product.

3. Methods of Preparation

This procedure is a modification of preparations of 3-phenylsydnone described earlier.^{2, 3} The dehydration of N-nitroso-N-phenylglycine has also been effected by the use of thionyl chloride and pyridine in dioxane,⁴ thionyl chloride in ether,⁴ trifluoroacetic anhydride in ether,⁴ and diisopropylcarbodiimide in water;⁵ or by reaction of the alkali metal salts of N-nitroso-N-phenylglycine with phosgene or benzenesulfonyl chloride in water⁵ or with acetyl chloride in benzene.⁴

4. Merits of the Preparation

The present procedure makes possible the preparation of large quantities of very pure 3-phenylsydnone without recrystallization. The earlier procedure² produced a tan or brown product which lost its color only after several recrystallizations. Slight variations in this procedure can be used to prepare a variety of 3-substituted and 3,4-disubstituted sydnone.

3-Phenylsydnone is the prototype of that class of mesoionic compounds called sydnone. On acidic hydrolysis it produces phenylhydrazine, whereas basic hydrolysis regenerates N-nitroso-N-phenylglycine. This sydnone undergoes a variety of electrophilic substitutions,^{3, 4, 6-19} including mercuration^{11, 13, 16} and formylation,¹⁹ with an ease comparable to thiophene, and a number of "1,3-dipolar cycloadditions" with numerous alkenes,^{15, 18} alkynes,¹⁷ and quinones⁸ to form, with loss of carbon dioxide, a variety of pyrazole derivatives.

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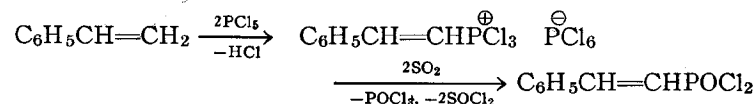
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STYRYLPHOSPHONIC DICHLORIDE

(Phosphonic dichloride, styryl-)



Submitted by R. SCHMUTZLER¹

Checked by WILLIAM G. DAUBEN and DAVID A. COX

1. Procedure

The reaction is conducted in a 500-ml. three-necked flask equipped with a sealed mechanical stirrer, a dropping funnel, and a reflux condenser carrying a drying tube. The flask is flushed with dry nitrogen, and 104 g. (0.50 mole) of phosphorus pentachloride in 150 ml. of dry benzene is added. The mixture is cooled in an ice bath (Note 1) and stirred while a solution of 26 g. (0.25 mole) of styrene in 50 ml. of dry benzene is added

through the dropping funnel during a period of 30 minutes. A dense crystalline solid begins to form immediately, and after the addition is completed the mixture is stirred for 30 minutes at room temperature. The dropping funnel is replaced by a gas-inlet tube which is connected to a cylinder of sulfur dioxide through a wash bottle containing concentrated sulfuric acid. Sulfur dioxide is bubbled through the stirred mixture until all the precipitate is dissolved. The mildly exothermic reaction is controlled by occasionally cooling the reactants with an ice bath. The benzene solvent is removed from the clear solution under reduced pressure, and the residue is distilled at reduced pressure from a Claisen flask with Vigreux indentations. The yield of styrylphosphonic dichloride is 49–52 g. (89–94%), b.p. 107–110° (0.2 mm.). The distillate solidifies during or after the distillation, m.p. 71–72°.

2. Note

1. Care must be taken not to freeze the benzene before the styrene is added.

3. Methods of Preparation

Styrylphosphonic dichloride has been prepared by the addition of phosphorus pentachloride to styrene with subsequent reaction of the adduct with phosphorus pentoxide² or sulfur dioxide.^{3, 4}

4. Merits of the Preparation

The addition reaction of phosphorus pentachloride to styrene and its derivatives provides a convenient route to styrylphosphonic acids and their derivatives.^{2–7} The styrene phosphorus pentachloride adduct also can be reduced with phosphorus to give the corresponding dichlorophosphine.^{4, 8}

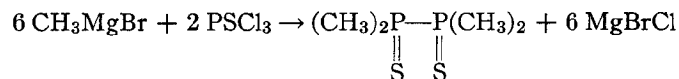
The behavior of phosphorus pentachloride toward carbon-carbon multiple bonds has received considerable attention, and the procedure described represents but one example of a wide variety of derivatives of unsaturated phosphonic acids which are accessible. Indene was the first olefinic compound to be reacted

with phosphorus pentachloride,⁹ and the reaction of phosphorus pentachloride with other unsaturated compounds has been described.^{2–6, 10–13} More recent examples include the reaction of phosphorus pentachloride with vinyl ethers^{14–16} and vinyl thioethers,¹⁷ providing access to β -alkoxy- and β -alkylmercaptovinylphosphonic and phosphonothioic acid derivatives.

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TETRAMETHYLBIPHOSPHINE DISULFIDE

(Diphosphine, tetramethyl-, disulfide)

Submitted by G. W. PARSHALL¹

Checked by W. S. WADSWORTH and WILLIAM D. EMMONS

1. Procedure

A 3-l. round-bottomed flask equipped with mechanical stirrer, condenser (surmounted by a drying tube), thermometer, and addition funnel is charged with 800 ml. of 3*M* methylmagnesium bromide solution (2.4 moles) (Note 1) and 600 ml. of anhydrous ether. The solution is stirred and cooled to 0–5° while a solution of 135 g. (83 ml., 0.80 mole) of thiophosphoryl chloride (Note 2) in 85 ml. of ether is added over a period of 3 hours. A thick white precipitate forms during the course of the addition. After completion of the addition, the reaction mixture is poured onto 500 g. of ice in a 4-l. beaker. Sulfuric acid (900 ml. of 10% solution) is added over a period of 20 minutes with gentle stirring. The mixture is filtered, and the white solid product is washed with 4 l. of water and recrystallized from 2 l. of ethanol. The product is dried over phosphorus pentoxide in a vacuum desiccator to give 50–55 g. (67–74%) of white crystalline tetramethylbiphosphine disulfide, m.p. 223–227° (Note 3). Evaporation of the mother liquor to a volume of 900 ml. gives an additional 3 g. of tetramethylbiphosphine disulfide, m.p. 222–225°.

2. Notes

1. A suitable 3*M* solution of methylmagnesium bromide in diethyl ether can be purchased from Arapahoe Chemical Co., Boulder, Colorado.

2. Although practical grade thiophosphoryl chloride obtained from Eastman Organic Chemicals will serve in this reaction, a much cleaner product is obtained if the thiophosphoryl chloride is redistilled (b.p. 122–123°).

3. Tetramethylbiphosphine disulfide melts sharply at 227° when pure, but the material obtained as described above is satisfactory for most reactions.

3. Methods of Preparation

Tetramethylbiphosphine disulfide has been prepared by reaction of methylmagnesium halides with thiophosphoryl chloride.^{2–4}

4. Merits of the Preparation

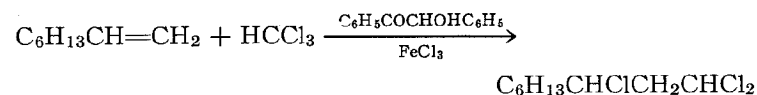
Tetramethylbiphosphine disulfide is an extremely versatile intermediate for the preparation of compounds containing two methyl groups on phosphorus, for example, dimethylphosphine.⁵ Most other methods for the preparation of such compounds give large amounts of mono- and trimethylated by-products. Tetramethylbiphosphine disulfide has been converted in high yields to dimethylphosphinic acid,^{3, 4} dimethylphosphinyl chloride,^{4, 6} and dimethylchlorophosphine.⁷ Other tetraalkylbiphosphine disulfides have been converted to tetraalkylbiphosphines, dialkylthiophosphoryl bromides, and dialkylphosphinic anhydrides.⁸ Addition of tetramethylbiphosphine disulfide to ethylene followed by desulfurization gives tetramethylethylenediphosphine, a powerful chelating agent.⁹ Other alkyl Grignard reagents also react with thiophosphoryl chloride under the conditions of the present procedure to give the corresponding tetraalkylbiphosphine disulfides in high yield.^{5, 10}

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1,1,3-TRICHLORO-*n*-NONANE

(Nonane, 1,1,3-trichloro-)



Submitted by D. VOFSI and M. ASSCHER¹
 Checked by S. N. EGE and PETER YATES

1. Procedure

A solution of 0.54 g. (2 mmoles) of ferric chloride hexahydrate and 0.33 g. (3 mmoles) of diethylammonium chloride (Note 1) in 5 g. of methanol is added to a solution of 11.2 g. (0.1 mole) of 1-octene (Note 2) and 0.42 g. (2 mmoles) of benzoin (Note 3) in 36 g. (0.3 mole) of chloroform (Note 4). The resulting homogeneous mixture is introduced into a Carius tube of about 100-ml. capacity. Air is displaced by dropping a few pieces of dry ice into the tube (Note 5). The tube is sealed (Note 6), heated to 130°, kept at that temperature for 15 hours, cooled to room temperature (Note 7), and opened. The contents of the tube are transferred to a separatory funnel, and the tube is rinsed with about 10 ml. of chloroform. The reaction mixture is washed with 40 ml. of water. The aqueous solution is extracted with 10 ml. of chloroform, and the extract is added to the original chloroform layer. Solvent is distilled at atmospheric pressure (bath temperature up to 130°). The distillation flask is allowed to cool, and distillation is continued at 25 mm. (bath temperature up to 120°) (Note 8). The flask is cooled again, and distillation is continued to dryness at 0.1 mm. (bath temperature up to 150°), giving crude 1,1,3-trichloro-*n*-nonane (19.4 g.) as a yellow oil, b.p. 60–85° (0.1 mm.), n_D^{25} 1.4650. The purity of this product is 95% (Note 9), and the actual yield is 80%. Frac-

tionation of this material through a 13-in. Vigreux column gives 15 g. (64%) of pure, colorless 1,1,3-trichloro-*n*-nonane, b.p. 61–62° (0.1 mm.), n_D^{25} 1.4640 (Notes 10 and 11).

2. Notes

1. Pure diethylammonium chloride can be obtained from Fluka A. G., Buchs, S. G., Switzerland. If this salt is omitted, somewhat lower yields (about 75%) of adduct are obtained.

2. Phillips 1-octene of 99% minimum purity was used; however, it was freed of peroxide by percolating through acid-washed alumina.

3. Benzoin, Eastman Organic Chemicals, practical grade, can be used directly.

4. Reagent grade chloroform is used.

5. If air is not displaced before sealing, there is an induction period of about 1 hour.

6. The Carius tube has a short piece (about 4 in.) of heavy-walled tube (8-mm. external diameter) sealed to it. This greatly facilitates subsequent sealing and re-use of the tube. The solution is introduced by means of a funnel with a drawn-out stem.

7. On cooling, the contents of the tube separate into two layers.

8. Occasionally a few drops, consisting mainly of unconverted 1-octene, are collected. The receiver then must be changed before the distillation at 0.1 mm. is continued.

9. The purity was determined by gas chromatography (1.5-m. column packed with 25% silicone oil on Chromosorb W, at 180°, and a flow rate of 60 ml. of helium per minute). The yellow color, which is due to traces of benzil, may be removed by diluting the product with three times its volume of pentane, percolating the solution through a column of about 30 g. of acid-washed alumina, washing the alumina with 50 ml. of pentane, and distilling the pentane at atmospheric pressure. The residue, which is colorless, boils at 61–63° (0.1 mm.), n_D^{25} 1.4643; the recovery is 95%.

10. The checkers distilled the reaction product directly through a 4-in. Vigreux column to obtain 15.4–15.8 g. (66–68%) of colorless product, b.p. 95–97° (2.5 mm.), n_D^{25} 1.4632.

11. The submitters have found that the reaction may be carried out on a much larger scale in an autoclave. The reaction must be run in a glass liner. As the hot reaction mixture is homogeneous, the autoclave may be heated while standing upright. The liner may be filled to three-quarters of its capacity.

3. Methods of Preparation

The method described, which is the only one available for the direct preparation of 1,1,3-trichloroalkanes, is applicable to aliphatic olefins and gives good yields, especially with terminal olefins.² With styrene or butadiene, yields are much lower.

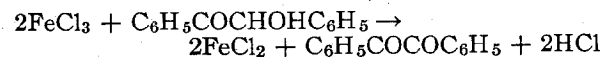
4. Merits of the Preparation

1,1,3-Trichloroalkanes are potential starting materials for the preparation of unsaturated aldehydes.³

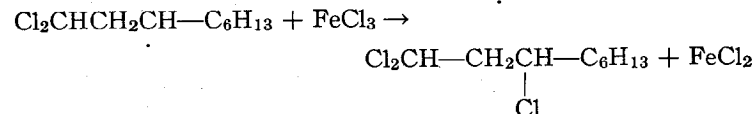
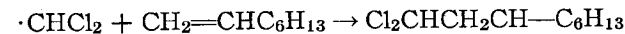
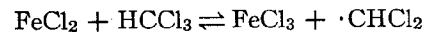
A similar method² can be used for the addition of carbon tetrachloride to nonpolymerizable olefins (e.g., 1-octene, 2-octene, 1-butene, 2-butene); pure adducts are obtained in yields of over 90% if the components are allowed to react at 100° for 6 hours. Adducts of carbon tetrachloride with vinylic monomers (styrene, butadiene, acrylonitrile, methyl acrylate, etc.) can be prepared in good yields by substituting cupric chloride dihydrate in acetonitrile for ferric chloride hexahydrate and benzoin.

In ordinary homolytic reactions (as distinguished from the reaction described here), chloroform adds to the double bond in the sense $\text{H}-\text{CCl}_3$.⁴ Bromodichloromethane adds in the sense $\text{Br}-\text{CHCl}_2$,³ similar to the orientation of chloroform additions in the present method ($\text{Cl}-\text{CHCl}_2$). The present method has the advantage of giving high yields while using cheap reagents, and it is thought to proceed as shown in the following equations.

Initiation



Propagation

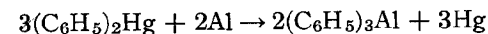


Carbon tetrachloride can be substituted for chloroform in this reaction when the cupric chloride modification described above is used.

1. Plastics Research Laboratory, Polymer Department, The Weizmann Institute of Science, Rehovoth, Israel.
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TRIPHENYLALUMINUM

(Aluminum, triphenyl-)



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Checked by R. D. LIPSCOMB and B. C. MCKUSICK

1. Procedure

Caution! Triphenylaluminum and its etherate undergo decomposition in the presence of air and moisture. Upon contact with water, vigorous heat evolution and sparking have been observed.

A 500-ml. one-necked flask with a side arm to admit nitrogen is fitted with a reflux condenser protected at the top by a T-tube through which nitrogen is slowly passed during the entire reaction (Note 1). In the flask there is placed 12 g. (0.44 g. atom) of aluminum wool (Note 2), and the system is thoroughly dried by flaming (Note 3) and then cooled to room temperature. A posi-

tive pressure of nitrogen is maintained in the system by admission of the gas through the side arm while the flask is detached from the condenser, stoppered, and transferred to a nitrogen-filled dry box. To the flask there is added 80 g. (0.23 mole) of diphenylmercury (Note 4) which is spread evenly on top of the aluminum wool, followed by 340 ml. of sodium-dried xylene. The flask is stoppered, returned to the condenser, and immersed in a preheated oil bath, which is maintained at 140–150°. The reaction mixture is allowed to reflux for 24 hours, the water drained from the condenser, and the top of the condenser is connected to a vacuum system through a trap cooled in dry ice. The xylene is distilled by gradually reducing the pressure to 20–30 mm. The flask is cooled to room temperature and nitrogen readmitted.

The flask is returned to the dry box, and the nearly dry solid that remains in it is transferred to an extraction thimble (123 mm. x 43 mm.) previously dried in a vacuum oven. The product is extracted in a dried Soxhlet apparatus (250 mm. x 50 mm.) with 250 ml. of dry ether (Note 5) in a carefully dried 300-ml. flask. The extraction is continued for 15–20 hours (Note 6), during which time white crystals of triphenylaluminum etherate form in the flask. The flask and its contents are placed in a dry box, the ether is decanted, and the crystals are washed several times by decantation with small portions of dry ether. The triphenylaluminum etherate is dried at 25° under reduced pressure; m.p. 126–130°. The ether of crystallization is removed by heating the etherate at 150° (0.1 mm.) for about 13 hours (Note 7). Pure triphenylaluminum, m.p. 229–232°, is obtained; yield 23–27 g. (59–70%).

2. Notes

1. All operations are conducted in an atmosphere of prepurified nitrogen or in a nitrogen-filled dry box. A positive nitrogen pressure is maintained in the flask during all transfers and additions. Prepurified nitrogen is available from Matheson Co., East Rutherford, New Jersey.

2. Suitable aluminum wool is available from Custom Scientific Instrument Inc., Kearney, New Jersey. It is thoroughly cleaned

with both methylene chloride and ether and dried before use.

3. All glassware used in this preparation must be dry. Flaming out while purging with prepurified nitrogen is sufficient.

4. Suitable diphenylmercury is available from Orgmet, Hampstead, New Hampshire, or it can be prepared by the procedure of Gilman and Brown.²

5. A new container of anhydrous ether from Mallinckrodt Chemical Works or Merck and Co. is satisfactory.

6. At the end of the extraction the residual aluminum wool should be disposed of very carefully because it is in a highly reactive condition. As the ether evaporates, the aluminum wool oxidizes rapidly and becomes quite hot. In one run, 84% of the theoretical amount of metallic mercury was liberated during this oxidation.

The checkers evaporated the ether in a stream of nitrogen, then allowed air to diffuse in gradually through a small opening during 2 days. The residue was then inert.

7. During this operation the etherate melts, effervesces, and then solidifies. The etherate sublimes to a small extent; this can be counteracted by immersing the flask in an oil bath only part way during the first half of the heating, and finally immersing it to the bottom of its neck.

3. Methods of Preparation

The general procedure for this reaction, which was first reported by Friedel and Crafts,³ is essentially that of Hilpert and Grüttner⁴ as modified by Gilman and Marple.⁵ Upon laboratory examination of these methods, only water-reactive gums and tars were isolated. Nesmeyanov and Novikova⁶ reported the preparation of triphenylaluminum by a similar method, but worked on a test-tube scale and did not report a yield. Wittig and Wittenberg⁷ prepared crystalline triphenylaluminum in 43% yield by the action of phenyllithium on aluminum chloride. In most of the procedures found, the triphenylaluminum was used in solution; hence crystalline material was not isolated.

When aluminum wool was substituted for strips of aluminum foil, a 20% yield of triphenylaluminum was obtained. This yield

was increased to 70% by the extractive isolation described above. An alternative method of isolation and purification, that of Krause and Polack,⁸ was not attempted because of the lack of experimental detail and the complexity of the apparatus.

4. Merits of the Preparation

Triphenylaluminum is useful as a component of catalyst systems for ionic or coordination polymerization of vinyl compounds. This preparation of the material in solid form enables the purity of the compound to be easily determined. The availability of solid triphenylaluminum permits the user a choice of solvents for a reaction, and a variety of concentrations of the reagent. Storage and dispensation of the reagent are more convenient in the solid form.

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SUBJECT INDEX

(This index comprises material from Volume 45 only; for previous volumes see Collective Volumes 1 through 4 and Volume 44.)

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

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ORGANIC SYNTHESSES

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

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NOMENCLATURE

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

SUBMISSION OF PREPARATIONS

Chemists are invited to submit for publication in *Organic Syntheses* procedures for the preparation of compounds which are of general interest, as well as procedures which illustrate synthetic methods of general utility. It is fundamental to the usefulness of *Organic Syntheses* that submitted procedures represent optimum conditions, and the procedures should have been checked carefully by the submitters, not only for yield and physical properties of the products, but also for any hazards that may be involved. Full details of all manipulations should be described, and the **range** of yields should be reported rather than the maximum yield obtainable by an operator who has had considerable experience with the preparation. For each solid product the melting-point **range** should be reported, and for each liquid product the **range** of boiling point and refractive index should be included. In some instances, it is desirable to include additional physical properties of the product, such as ultraviolet, infrared, or nuclear magnetic resonance spectra. The methods of preparation or sources of the reactants should be described in notes, and the physical properties (such as boiling point, index of refraction, melting point) of the reactants should be included except where rather standard commercial grades are specified.

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Additions, corrections, and improvements to the preparations previously published are welcomed and should be directed to the Secretary.

EDITOR'S PREFACE

The basic format of *Organic Syntheses* has remained essentially unchanged during the publication of the previous forty-four volumes; however, the content of the books has undergone gradual change. More examples of new and general types of reactions and compounds, and fewer examples of the preparation of a specific compound, have been provided. In the late 1950's another change occurred which went unnoticed: a more extensive index was prepared for each volume; and in this process, more pages of each volume were needed for the cumulative index. For the general size and the cost of each volume to remain approximately constant, the last volume of a ten-year period would have little space for new preparations. To circumvent this undesirable situation the Editors have decided to let the collective index cover only Volumes 40 to 44 and to begin a new five-year collective index with this volume. However, as in the past, the collective volume which will combine Volumes 40 to 49 will have a complete index for those volumes.

Like earlier volumes, this one contains the preparation of compounds of specific interest and of compounds which illustrate new and general synthetic reactions. In the latter category can be mentioned these preparations: the selective cleavage of a carbomethoxy group with lithium iodide in 2,4,6-collidine (2-benzylcyclopentanone); the oxidation of alcohols under mild conditions using a mixture of chromic acid and acetone, the "Jones reagent" (cyclooctanone and nortricyclanone); the oxidative coupling of monosubstituted acetylenes with cupric acetate-pyridine reagent, "the Glaser oxidative coupling" (diphenyldiacetylene); the reaction of the anion of triethylphosphonoacetate with ketones to prepare α,β -unsaturated esters (ethylcyclohexylideneacetate); the substitution of an angular methyl group of a steroid by the hypoiodite reaction (18,20-lactone of 3 β -acetoxy-20 β -hydroxy-5-pregnene-18-oic acid); the

reaction of an enamine with electrophilic olefins ($\Delta^{1(9)}$ -octalone-2); the preparation of cyclic isomers of diazo compounds, diazirines (3,3-pentamethylenediazirine); the generation of a benzyne using potassium *t*-butoxide in dimethylsulfoxide (phenyl *t*-butyl ether); and the preparation of 9-substituted phenanthrenes by photocyclization and oxidation of substituted stilbenes (9-phenyl-phenanthrene).

The members of the Editorial Board thank the chemists who contribute the preparations which make *Organic Syntheses* possible. The Board welcomes suggestions from readers regarding not only specific chemical preparations but also any changes which would make this publication more useful, for it is the utility of this series that warrants its continuance.

WILLIAM G. DAUBEN

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