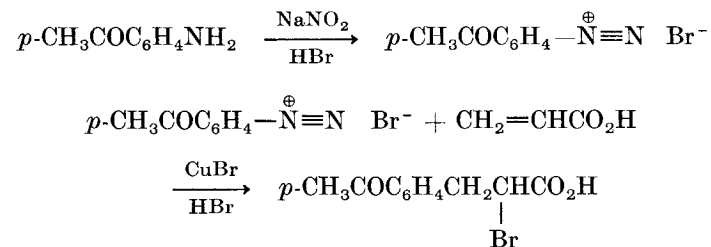


***p*-ACETYL- $\alpha$ -BROMOHYDROCINNAMIC ACID**

(Hydrocinnamic acid, *p*-acetyl- $\alpha$ -bromo-)



Submitted by GEORGE H. CLELAND<sup>1</sup>

Checked by MICHAEL J. UMEN and HERBERT O. HOUSE

**1. Procedure**

*Caution! Since bromoacetone, a powerful lachrymator, is produced as a by-product in this preparation, the reaction should be performed in a hood.*

A tared 500-ml. two-necked round-bottomed flask is equipped with a magnetic stirring bar, a thermometer, and an ice-filled cooling bath. A solution of 13.5 g. (0.10 mole) of *p*-aminoacetophenone (Note 1) in 200 ml. of acetone is placed in the flask and stirred while 32 ml. (about 0.3 mole) of aqueous 48% hydrobromic acid is added. After the resulting solution has been cooled to 5–7°, it is stirred continuously while 20 ml. of an aqueous solution containing 6.90 g. (0.10 mole) of sodium nitrite is added rapidly (30 seconds) beneath the surface of the reaction solution by means of a hypodermic syringe or a long-stemmed dropping funnel. Stirring and cooling are continued until the exothermic reaction subsides (Note 2) and the reaction solution has cooled to 14–15°. Then 106 g. (100 ml., 1.47 moles) of acrylic acid (Note 3) is added. The resulting solution is again cooled to 14–15° with stirring and 0.10–0.11 g. (0.0007 mole) of copper(I) bromide (Note 4) is added. Stirring is continued during which time the solution darkens, and nitrogen evolution

is observed; the temperature of the reaction mixture is kept below 33° by use of the external cooling bath. As soon as the evolution of nitrogen has ceased (usually 20 minutes is sufficient), the reaction solution is concentrated under reduced pressure with a rotary evaporator to give a mixture weighing about 120–130 g. The residual brown suspension is mixed with 5 g. of decolorizing charcoal and 200 ml. of water and the resulting mixture is boiled for 3 minutes and then filtered while hot through a Büchner funnel containing Celite filter aid. The residue on the filter is washed with 100 ml. of boiling water, and the combined filtrates are diluted with 300 ml. of water. The resulting aqueous solution, from which the product begins to crystallize, is cooled in a water bath and then allowed to stand in a refrigerator (0–3°) for 24 hours to complete the crystallization of the crude product. The crystalline solid that separates is collected on a filter, washed with two 100-ml. portions of cold water, and then dried in the air. The crude product, a pale yellow solid amounting to 19.1–22.2 g., is recrystallized from 40 ml. of a 2:3 (v/v) formic acid-water mixture. The resulting crystals are collected on a filter, washed with 20 ml. of a cold mixture of formic acid and water (2:3 v/v), and dried in the air. The product amounts to 16.6–18.2 g. (61–67%) of white needles, m.p. 158–160°, which is sufficiently pure for most purposes. Three additional crystallizations from 20-ml. portions of a 2:3 (v/v) formic acid-water mixture give 15.2–16.0 g. (56–59%) (Note 5) of the pure *p*-acetyl- $\alpha$ -bromohydrocinnamic acid, m.p. 159–161° (Note 6).

## 2. Notes

1. Commercial grades of acetone and *p*-aminoacetophenone (Matheson Coleman and Bell or Aldrich Chemical Company, Inc.) were used without further purification.

2. The temperature of the reaction mixture rises to about 30° and then falls to 15° as stirring and cooling are continued. If this preparation were performed on a larger scale, it would probably be necessary to add the sodium nitrite solution over a longer period of time in order to control the temperature.

3. A freshly opened bottle of acrylic acid, obtained from Eastman Organic Chemicals, was used without further purification. The checkers encountered difficulty in attempting to use samples of acrylic acid that had been stored in partially filled bottles for long periods of time.

4. A reagent grade of copper(I) bromide, obtained from Fisher Scientific Company, was washed with acetone until the washings were colorless and then dried.

5. The combined filtrates from these recrystallizations can be concentrated to obtain an additional 1–2 g. of product.

6. The product has infrared absorption (KBr pellet) at 1735, 1645, and 1607  $\text{cm}^{-1}$  with an ultraviolet maximum (95% EtOH solution) at 252.5  $\text{m}\mu$  ( $\epsilon$  17,000). The sample has n.m.r. peaks ( $\text{CF}_3\text{CO}_2\text{H}$  solution) at 8.10 (doublet,  $J = 9$  Hz., 2H, aryl CH), 7.47 (doublet,  $J = 9$  Hz., 2H, aryl CH), 4.60 (triplet,  $J = 7.5$  Hz., 1H, CHBr), 3.2–3.9 (multiplet, 2H, benzylic  $\text{CH}_2$ ), and 2.78 p.p.m. (singlet, 3H,  $\text{CH}_3\text{CO}$ ). The mass spectrum has weak molecular peaks at  $m/e$  270 and 272 with the following relatively abundant fragment peaks:  $m/e$  (rel. int.), 191 (73), 175 (100), 131 (52), 103 (40), 77 (55), and 51 (43). The product gives a deep red color when treated with sodium nitroprusside and aqueous base; this color changes to dark blue upon acidification with acetic acid.

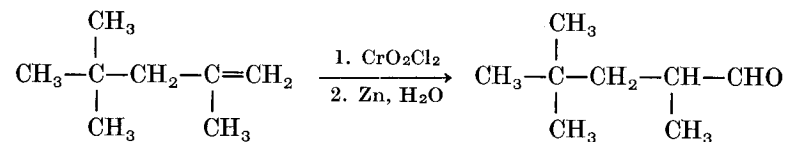
## 3. Discussion

This procedure has been used to prepare a variety of substituted  $\alpha$ -bromohydrocinnamic acids;<sup>2</sup> *p*-acetyl- $\alpha$ -bromohydrocinnamic acid was prepared for the first time by this method. The method illustrates a typical application of the Meerwein reaction for the arylation of unsaturated substrates.<sup>3</sup> In this reaction a catalytic amount of a copper(I) salt is used to reduce an aryl diazonium salt forming an aryl radical and a copper(II) halide. Addition of the aryl radical to an unsaturated substrate forms an alkyl radical that is reoxidized by the copper(II) halide present forming an alkyl halide and regenerating the copper(I) salt catalyst. In this preparation, the product, an  $\alpha$ -bromo acid, is formed in an acidic reaction mixture and dehydrohalogenation does not occur. However, dehydrohalogenation

of the intermediate halide is often observed in analogous reactions performed under neutral or basic reaction conditions.<sup>3</sup> The use of the Meerwein reaction to form ultimately 1-(*p*-nitrophenyl)-1,3-butadiene by the addition of an intermediate aryl radical to 1,3-butadiene followed by dehydrohalogenation of the initially formed alkyl halide is illustrated in *Organic Syntheses*.<sup>4</sup>

1. Department of Chemistry, Occidental College, Los Angeles, California 90041.
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#### ALDEHYDES BY OXIDATION OF TERMINAL OLEFINS WITH CHROMYL CHLORIDE: 2,4,4-TRIMETHYLPENTANAL



Submitted by FILLMORE FREEMAN, RICHARD H. DUBOIS,  
and THOMAS G. McLAUGHLIN<sup>1</sup>  
Checked by GRAHAM HAGENS and PETER YATES

#### 1. Procedure

In a 5-l. three-necked flask fitted with a mechanical stirrer, a thermometer, and a dropping funnel equipped with a calcium chloride drying tube are placed 112.2 g. (1.00 mole) of freshly distilled 2,4,4-trimethyl-1-pentene (Note 1) and 1 l. of methylene chloride (Note 2). The flask is immersed in an ice-salt bath, and the stirred solution is cooled to 0–5°. A solution of 158 g. (1.02 moles) (Note 3) of freshly distilled chromyl chloride (Note 4) in 200 ml. of methylene chloride (Note 5) is added dropwise with stirring from the dropping funnel while the temperature is maintained at 0–5° (Note 6). The reaction mixture is stirred for 15 minutes, and 184 g. of 90–95% technical

grade zinc dust (Note 7) is added. The mixture is stirred for 5 minutes, 1 l. of ice water and 400 g. of ice are added as rapidly as possible (Note 8), and the mixture is stirred for an additional 15 minutes. The ice-salt bath is replaced by a heating mantle, and the flask is fitted for steam distillation. After distillation of the methylene chloride the residue is steam distilled (Note 9). The distillate is transferred to a separatory funnel, the organic layer is separated, and the aqueous layer is washed with three 50-ml. portions of methylene chloride. The combined organic phases are distilled (Note 10) through a 56-cm. vacuum-jacketed Vigreux column to remove the solvent. The product is transferred to a 250-ml. round-bottomed flask and distilled. After removal of a small amount of methylene chloride, the fraction boiling at 45–52° (15 mm.) is collected to give 90–100 g. (70–78%) (Note 11) of 2,4,4-trimethylpentanal.

#### 2. Notes

1. The alkene is available from Aldrich Chemical Company, Inc., or Phillips Petroleum Company and can be used without distillation.
2. The material available from Matheson Coleman and Bell or Eastman Organic Chemicals is satisfactory except as explained in Note 5.
3. Since chromyl chloride is easily hydrolyzed, a slight excess is used.
4. The fraction, b.p. 115.5–116.5°, is used. Chromyl chloride is available from Alfa Inorganics, Inc.
5. Chromyl chloride tends to react slowly with the commercially available methylene chloride. This can be avoided with a slight increase in yield if the methylene chloride used to dissolve the chromyl chloride is distilled through a 15–20 cm. Vigreux column immediately before use.
6. The time required for the addition is about 60 minutes.
7. This approximate fivefold excess is necessary to reduce the chromium higher valent salts and thereby eliminate overoxidation and double bond cleavage. The zinc dust used was obtained from Allied Chemical Corporation.

8. The temperature usually increases to 8–10°.
9. Steam distillation is discontinued when the distillate gives a negative test with 2,4-dinitrophenylhydrazine reagent.
10. It is not necessary to dry the organic phase.
11. The checkers, working at two-thirds scale, obtained the product in 70–71% yield.

### 3. Discussion

2,4,4-Trimethylpentanal has been prepared by the catalytic isomerization of 1,2-epoxy-2,4,4-trimethylpentane in the liquid and in the gas phase (77–92%),<sup>2</sup> and by the oxidation of 2,4,4-trimethyl-1-pentene with chromium trioxide in acetic anhydride.<sup>3</sup> Although the catalytic isomerization of the epoxide<sup>2</sup> gives 2,4,4-trimethylpentanal in good yield, this requires the epoxidation of the alkene as the first step. The chromyl acetate and chromic acid oxidative methods of preparation give unsatisfactory yields.<sup>3</sup> In the preparation described here, 2,4,4-trimethylpentanal is obtained from the alkene in good yield in one step. Also, this preparation illustrates a general and convenient procedure for the oxidation of 2,2-disubstituted-1-alkenes (Table I) directly to unstable and reactive aldehydes.<sup>4</sup> The reaction is very fast and the aldehyde is the major product.

TABLE I  
ALDEHYDES BY OXIDATION OF TERMINAL OLEFINS  
WITH CHROMYL CHLORIDE

Alkene	Aldehyde	Yield, %
4,4-Dimethyl-2-neopentyl-1-pentene	4,4-Dimethyl-2-neopentylpentanal	80.8 <sup>a</sup>
2-Phenylpropene	2-Phenylpropanal	60.0 <sup>b</sup>
1,1-Diphenylethylene	2,2-Diphenylethanal	62.7 <sup>b</sup>

<sup>a</sup> Reference 4.

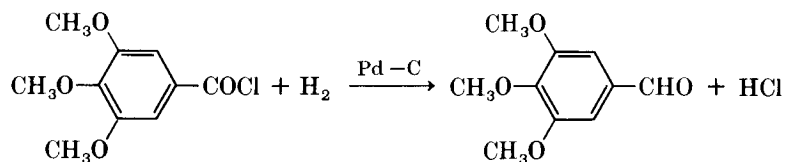
<sup>b</sup> Reference 5.

4,4-Dimethyl-2-neopentylpentanal,<sup>6</sup> 2-phenylpropanal,<sup>7</sup> and 2,2-diphenylethanal<sup>8</sup> are generally prepared by isomerization of the corresponding epoxide and/or by multistep syntheses.

In contrast to the relative simplicity of the chromyl chloride oxidation of 2,2-disubstituted-1-alkenes to aldehydes, the chromyl acetate and chromic acid oxidations generally lead to epoxides, acids, and carbon-carbon double bond cleavage. For example, chromyl acetate oxidizes 4,4-dimethyl-2-neopentyl-1-pentene primarily to 1,2-epoxy-4,4-dimethyl-2-neopentylpentane in low yield,<sup>9</sup> and chromic acid oxidizes the alkene principally to 4,4-dimethyl-2-neopentylpentanoic acid.<sup>6,10</sup>

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ALDEHYDES FROM ACID CHLORIDES BY MODIFIED  
ROSENMUND REDUCTION:  
3,4,5-TRIMETHOXYBENZALDEHYDE



Submitted by A. I. RACHLIN, H. GURIEN, and D. P. WAGNER<sup>1</sup>  
Checked by JAMES H. SHERMAN and RICHARD E. BENSON

### 1. Procedure

A pressure vessel (Note 1) is charged in order with 600 ml. of dry toluene (Note 2), 25 g. (0.3 mole) of anhydrous sodium acetate (Note 3), 3 g. of dry 10% palladium-on-carbon catalyst (Note 4), 23 g. (0.1 mole) of 3,4,5-trimethoxybenzoyl chloride (Note 5), and 1 ml. of Quinoline S (Note 6). The pressure vessel is flushed with nitrogen, sealed, evacuated briefly, and pressured to 50 p.s.i. with hydrogen. The mixture is shaken with 50 p.s.i. of hydrogen for 1 hour at room temperature (Note 7) and then is heated at 35–40° for 2 hours. Agitation is continued overnight while the reaction mixture cools to room temperature. The pressure on the vessel is released, the vessel is opened, and the mixture is filtered through 10 g. of Celite filter aid, and the insoluble material is washed with 25 ml. of toluene. The combined filtrates are washed with 25 ml. of 5% sodium carbonate solution and then with 25 ml. of water. The toluene solution is dried over 5 g. of anhydrous sodium sulfate, and the drying agent is recovered by filtration. The filtrate is concentrated by distillation at reduced pressure using a water aspirator. The residue (Note 8) is distilled through a 10-cm. Vigreux column with warm water circulating through the condenser to prevent crystallization of the distillate to yield 12.5–16.2 g. (64–83%) of

### 2. Notes

1. Both glass-lined and stainless-steel autoclaves have been used successfully. The checkers used a 1.2-1. Hastelloy autoclave.

2. Reagent-grade toluene was heated at reflux to remove a small fore-run and then allowed to cool.

3. Anhydrous sodium acetate was dried in a vacuum oven at 115° for 48 hours. The use of less than 3 moles of sodium acetate per mole of acid chloride results in a lower yield of product.

4. A catalyst available from Engelhard Industries was used. The catalyst was dried in a vacuum oven at 115° for 48 hours. *Caution! Palladium-on-carbon is pyrophoric, and vacuum drying increases this hazard. Catalysts kept in the oven for longer periods of time were extremely pyrophoric.*

5. The acid chloride or the acid may be purchased from Aldrich Chemical Company, Inc. The acid chloride must be pure (99% minimum by gas chromatography analysis) whether purchased or prepared. Purification was effected by recrystallization from Skellysolve B.

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7. Repressuring with hydrogen is required during this period. The amount of repressuring required is dependent upon the free space of the pressure vessel. The submitters report lower yields if the pressure falls below 30 p.s.i. No further repressuring is made at the end of 1 hour.

8. The crude aldehyde (prior to distillation) is sufficiently pure for most purposes. Isolation of the aldehyde may also be achieved by means of the bisulfite-addition compound.<sup>2</sup>

9. The product shows a strong infrared band (KBr wafer) at 1690 cm.<sup>-1</sup> (C=O). The n.m.r. spectrum (carbon tetrachloride solution) has peaks at 3.84 (singlet, 3H), 3.87 (singlet, 6H), 7.03 (singlet, 2H), and 9.76 p.p.m. (singlet, 1H).

10. The submitters state that the aldehyde is obtained in 78–84% yield when the reaction is conducted on a scale 5

times that described above. The amount of catalyst and Quinoline S need not be increased proportionately. The pressure vessel is charged with 3 l. of dry toluene, 123 g. of anhydrous sodium acetate, 10 g. of dry 10% palladium-on-carbon catalyst, 115 g. of 3,4,5-trimethoxybenzoyl chloride, and 4 ml. of Quinoline S.

### 3. Discussion

3,4,5-Trimethoxybenzaldehyde has been prepared by the classical Rosenmund<sup>3-5</sup> reduction, from 5-hydroxyvanillin by methylation,<sup>6</sup> and by oxidation of 3,4,5-trimethoxybenzyl alcohol.<sup>7</sup>

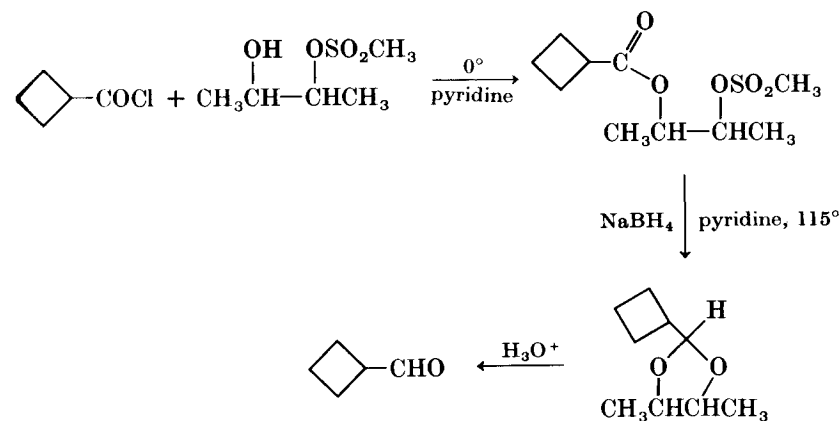
The normal Rosenmund reduction has often been used for small-scale reactions, but for large preparations it has the following disadvantages: long reaction cycles at elevated temperatures, inefficient use of hydrogen, the hazard of passing hydrogen through and away from a hot reaction, the use of relatively high catalyst to substrate ratios, and the necessity of monitoring the evolved hydrogen chloride as a means of following the reaction. These shortcomings have been eliminated by carrying out the reaction in a closed system at low pressure in the presence of a hydrogen chloride acceptor.

The reaction has been carried out on large- and small-scale batches (Note 10). This modification,<sup>8</sup> as exemplified by 3,4,5-trimethoxybenzaldehyde<sup>9</sup> such as 3,4-dimethylbenzaldehyde<sup>10</sup> (90% yield), 3-benzyloxy-4,5-dimethoxybenzaldehyde<sup>11</sup> (88% yield, with retention of the benzyl group), and 3-methoxy-4-nitrobenzaldehyde<sup>12</sup> (62% yield, with retention of the nitro group).

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### ALDEHYDES FROM ACID CHLORIDES BY REDUCTION OF ESTER-MESYLATES WITH SODIUM BOROHYDRIDE: CYCLOBUTANECARBOXALDEHYDE



Submitted by M. ROSS JOHNSON and BRUCE RICKBORN<sup>1</sup>  
Checked by SAUL C. CHERKOFKY and RICHARD E. BENSON

### 1. Procedure

**A. Erythro-2,3-butanediol monomesylate.** A 2-l. round-bottomed flask is equipped with a 1-l. dropping funnel to which is attached a drying tube containing calcium chloride. A magnetic stirring bar is placed in the flask and a solution of 48.0 g. (0.50 mole) of methanesulfonic acid (Note 1) in 500 ml. of anhydrous ether is added. Stirring is begun, and the flask is cooled in an ice-water bath while a solution of 37 g. (0.515 mole)

of *trans*-2-butene oxide (Notes 2 and 3) in 500 ml. of anhydrous ether is added over a period of 3–4 hours (Note 4). After 6 hours the cooling bath is removed and the mixture is stirred an additional 12 hours. The ether and any excess epoxide are removed at 25° by use of a rotary evaporator attached to a water aspirator to give 83–84 g. (99–100%) of *erythro*-2,3-butanediol monomesylate as a clear, colorless, somewhat viscous liquid (Note 5).

B. *Erythro*-3-methanesulfonyloxy-2-butyl cyclobutanecarboxylate. A 500-ml. round-bottomed flask is equipped with a 50-ml. dropping funnel, and a magnetic stirring bar is placed in the flask. The flask is cooled in an ice-water bath and 35.3 g. (0.21 mole) of *erythro*-2,3-butanediol monomesylate (from Part A) and 150 ml. of dry pyridine are added. Stirring is begun, and 23.7 g. (0.20 mole) of cyclobutanecarbonyl chloride (Note 6) is added over a period of 1 hour. The cooling bath is removed, and stirring is continued for 8 hours. The mixture is added to 500 ml. of ether, and the resulting solution washed three times with 250-ml. portions of 3*N* sulfuric acid. The pyridine-free solution is washed with 250 ml. of a saturated sodium bicarbonate solution and then with 250 ml. of water. The ether solution is dried over 2 g. of anhydrous magnesium sulfate. The solvent is removed by use of a rotary evaporator at 25° to give 45.1–48.0 g. (90–96%) of *erythro*-3-methanesulfonyloxy-2-butyl cyclobutanecarboxylate as a pale yellow, viscous liquid (Note 7).

C. 2-Cyclobutyl-*cis*-4-*trans*-5-dimethyl-1,3-dioxolane. A 2-l. three-necked round-bottomed flask is equipped with a mechanical stirrer, a 125-ml. dropping funnel, and a condenser to which is attached a nitrogen line with a bubbler device to permit maintenance of a positive pressure of nitrogen. Anhydrous pyridine (650 ml.) and 5 g. (0.125 mole) of sodium borohydride (Note 8) are added to the flask, stirring is begun, and the mixture is heated at reflux. A solution of 25 g. (0.10 mole) of *erythro*-3-methanesulfonyloxy-2-butyl cyclobutanecarboxylate (from Part B) in 50 ml. of anhydrous pyridine is then added from the dropping funnel over a period of 30 minutes and heating at reflux is continued for 8 hours. After cooling, 50 ml. of water is added (some heat is evolved), and the mixture is transferred to a 4-l. separatory funnel with 1 l. of

pentane (Note 9), and 700 ml. of cold 3*N* sulfuric acid saturated with sodium chloride. The aqueous layer is separated and washed two times with 250-ml. portions of pentane. The pentane extractions are combined and washed with three 500-ml. portions of 3*N* sulfuric acid saturated with sodium chloride and finally with 500 ml. of a saturated sodium bicarbonate solution. The pentane solution is dried over 1 g. of anhydrous potassium carbonate, the pentane is removed by evaporation on a steam bath, and the product is distilled through a short Vigreux column to give 6.7–7.6 g. (43–49%) (Note 10) of 2-cyclobutyl-*cis*-4-*trans*-5-dimethyl-1,3-dioxolane, b.p. 79–83° (22 mm.) (Note 11).

D. *Cyclobutanecarboxaldehyde*. A 1-l. round-bottomed flask containing a magnetic stirring bar is fitted with a 60-cm. glass helix-packed column. To the flask are added 600 ml. of 3*N* sulfuric acid, 200 ml. of dimethylformamide (Note 12), and 20 g. (0.13 mole) of 2-cyclobutyl-*cis*-4-*trans*-5-dimethyl-1,3-dioxolane (from Part C). The mixture is heated to gentle reflux, and cyclobutanecarboxaldehyde is collected as a steam distillate, b.p. 86°. After the distillation of the oil has ceased, the product is transferred to a separatory funnel, and the lower layer of water is discarded. The oil is dissolved in 25 ml. of ether, and the solution is dried over anhydrous sodium sulfate. The product is distilled through a small Vigreux column. After removal of the ether, 6.2–6.7 g. (58–63%) of cyclobutanecarboxaldehyde is collected, b.p. 56–59° (120 mm.) (Note 13).

## 2. Notes

1. Methanesulfonic acid was obtained from Aldrich Chemical Company, Inc., and distilled prior to use. The fraction b.p. 140° (0.2 mm.) was used.

2. *trans*-2-Butene oxide was prepared by appropriate modification of the procedure of Reif and House.<sup>2</sup> In a 2-l. four-necked round-bottomed flask fitted with a mechanical stirrer, a 1-l. dropping funnel, a dry ice-acetone condenser, and a thermometer is placed 1 l. of *sym*-tetrachloroethane. The condenser is packed with a dry ice-acetone mixture, and the flask is cooled in an ice-methanol bath to –15°. One hundred

fifty-three grams (2.73 moles) of *trans*-2-butene (Phillips Petroleum Company, 99%) is distilled into the flask from a tared, chilled trap. Six hundred milliliters of 40% peracetic acid (FMC Corporation), to which has been added 30 g. sodium acetate to neutralize the sulfuric acid that is present, is added to the stirred solution from the dropping funnel over a period of 2 hours. The mixture is stirred at  $-15^{\circ}$  for another hour and then allowed to warm to room temperature. The mixture is poured into 1 l. of ice-cold water. The organic layer is separated and washed with 10% sodium carbonate solution and then with water. The organic layer is dried over magnesium sulfate, and the drying agent removed by filtration. Distillation of the filtrate through a 75-cm. spinning-band column gives 133 g. (68%) of *trans*-2-butene oxide as a colorless oil, b.p.  $52.5-55^{\circ}$ .

3. A slight excess of *trans*-2-butene oxide is used to assure complete utilization of methanesulfonic acid. The checkers' experiments indicated that the use of a 15% excess of the epoxide substantially reduced the amount of unreacted methanesulfonic acid present in the product and did not appear to interfere with the succeeding steps of this procedure.

4. This order of addition and dilution is required to avoid dimerization or polymerization of the epoxide.

5. No attempt was made to further purify this compound, which had a very characteristic n.m.r. spectrum (deuteriochloroform solution, external tetramethylsilane reference): 1.22 (doublet,  $J = 7.5$  Hz., 3H), 1.37 (doublet,  $J = 7.5$  Hz., 3H), 3.1 (singlet, 3H), 3.4 (singlet, OH, position variable), 4.0 (doublet of quartets;  $J = 4.0, 7.5$  Hz.; 1H), and 4.78 p.p.m. (doublet of quartets,  $J = 4.0, 7.5$  Hz.; 1H). A sample stored for several weeks at room temperature showed no change in its spectrum.

6. Cyclobutanecarbonyl chloride was obtained from Aldrich Chemical Company, Inc. It was distilled prior to use. The acid chloride can be prepared by the reaction of thionyl chloride with the corresponding acid (available from Aldrich) by the general procedure of Helferich and Schaefer.<sup>3</sup> The preparation of cyclobutanecarboxylic acid has been described in *Organic Syntheses*<sup>4</sup> and elsewhere.<sup>5</sup>

7. The n.m.r. spectrum (deuteriochloroform solution, external tetramethylsilane reference): 1.27 (doublet,  $J = 6.5$  Hz., 3H), 1.41 (doublet,  $J = 6.5$  Hz., 3H), 2.18 (multiplet, 6H), 3.10 (singlet, 3H), superimposed on 3.2 (multiplet, 1H), and 5.0 p.p.m. (multiplet, 2H). Infrared (chloroform solution):  $1725\text{ cm}^{-1}$ .

8. Commercial material from Matheson Coleman and Bell and recrystallized reagent gave comparable results. The yield is decreased by use of less than 1 mole of sodium borohydride per mole of mesylate.

9. Either purified pentane or Spectranalyzed pentane available from Fisher Scientific Company was used.

10. The submitter reports yields of 10–11 g. (64–71%). The checker obtained the dioxolane in 57% yield on conducting the experiment on a sixfold scale.

11. The n.m.r. spectrum (neat, external tetramethylsilane reference) 1.1 (two overlapping doublets,  $J = 6$  Hz., 6H), 1.7–2.0 (multiplet, 6H), 2.1–2.6 (multiplet, 1H), 3.2–3.8 (multiplet, 2H), and 4.94 p.p.m. (doublet,  $J = 5$  Hz., 1H).

12. This proportion of water to dimethylformamide is needed to assure solubility (hence facile reaction) of the acetal on heating at reflux.

13. The n.m.r. spectrum (neat, external tetramethylsilane reference): 1.4–2.4 (multiplet, 6H), 2.6–3.2 (multiplet, 1H), and 9.8 p.p.m. (doublet,  $J \approx 1.5$  Hz., 1H); infrared spectrum (carbon tetrachloride solution);  $1730\text{ cm}^{-1}$  ( $\text{C}=\text{O}$ ).

### 3. Discussion

Cyclobutanecarboxaldehyde has been prepared in very low yield by the Rosenmund reduction procedure.<sup>6</sup> A 46% yield of the 2,4-dinitrophenylhydrazone derivative has also been reported, with the aldehyde formed as an intermediate, in the reaction of the acid chloride and lithium tri-*t*-butoxyaluminum hydride at  $-78^{\circ}$  in diglyme.<sup>7</sup>


Of the several methods now available for the reduction of carboxylic acid derivatives to aldehydes, all require careful control of conditions to avoid overreduction or underreduction. The procedure described here is particularly convenient in that



the acetal, not subject to further reduction, is formed directly in the reducing medium.

The scope of the reaction is indicated in Table I. An interesting aspect of the reaction is that the rate of the borohydride

TABLE I  
ALDEHYDES FROM ESTER-MESYLATES

$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{C}-\text{O}-\text{CH}(\text{CH}_3)-\text{CH}(\text{CH}_3)-\text{OSO}_2\text{CH}_3 \\ \text{(A)} \end{array}$	$\longrightarrow \begin{array}{c} \text{O}-\text{CHCH}_3 \\   \\ \text{R}-\text{CH} \\   \\ \text{O}-\text{CHCH}_3 \\ \text{(B)} \end{array}$	$\longrightarrow \text{RCHO} \quad \text{(C)}$
Ester-Mesylates (A), R =	Acetal (B) Yield, % <sup>a</sup>	Aldehyde (C) Yield, % <sup>a</sup>
<i>n</i> -C <sub>5</sub> H <sub>11</sub> -	63	78
C <sub>6</sub> H <sub>5</sub> -	64	89
cyclo-C <sub>6</sub> H <sub>11</sub> -	75	93
(CH <sub>3</sub> ) <sub>3</sub> C-	77	50 <sup>b</sup>
C <sub>6</sub> H <sub>5</sub> CH=CH-	62	87 <sup>c,d</sup>
	67	81 <sup>c</sup>
cyclo-C <sub>3</sub> H <sub>5</sub> -	72	81

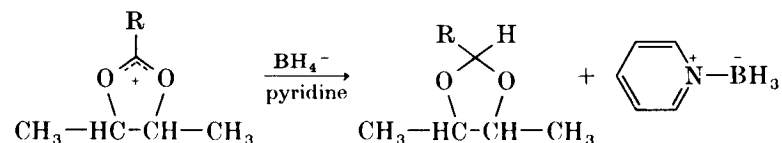
<sup>a</sup> Yield of distilled product; in several instances numerous runs were made, and the lowest yield is given.

<sup>b</sup> This acetal hydrolyzes quite slowly, and the relatively low yield of pivalaldehyde appears to be associated with this observation.

<sup>c</sup> Yields determined by gas chromatography analysis only.

<sup>d</sup> Fifteen percent of this product is the dihydro derivative, that is, the acetal of 3-phenylpropanal.

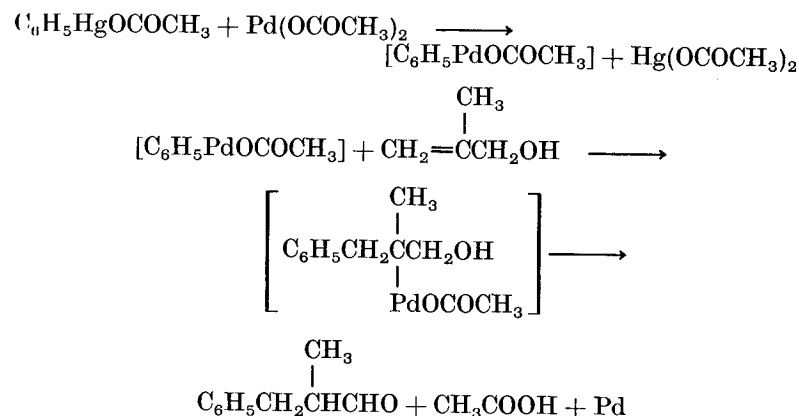
reduction step appears to be relatively insensitive to the substituent R. It is suggested that the reaction occurs with formation of an intermediate acyloxonium ion, which is rapidly converted to acetal by reaction with the borohydride ion. Pyridine-borane has been shown to be the other product



of this reaction; yield studies also indicate that only one hydride per borohydride ion is used efficiently in the formation of acetal.

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### ALDEHYDES FROM ALLYLIC ALCOHOLS AND PHENYLPALLADIUM ACETATE: 2-METHYL-3-PHENYLPROPIONALDEHYDE



Submitted by R. F. HECK<sup>1</sup>

Checked by ROBERT A. CLEMENT and RICHARD E. BENSON

#### 1. Procedure

A slurry comprised of 33.6 g. (0.10 mole) of commercial phenylmercuric acetate, 200 ml. of acetonitrile, and 14.4 g. (17 ml., 0.2 mole) of methallyl alcohol (Note 1) is prepared in a

500-ml. three-necked flask fitted with a mechanical stirrer, a condenser, and a thermometer. The slurry is stirred and cooled in an ice bath, and 22.4 g. (0.1 mole) of powdered palladium acetate (Note 2) is added over 1 minute. Stirring is continued with cooling for 1 hour and then at room temperature for 3 more hours (Note 3). The temperature of the reaction mixture reaches a maximum of 27° after removal of the ice bath.

The black reaction mixture is diluted with about 100 ml. of ether and poured onto 200 g. of ether-wet alumina (Woelm, Activity Grade 1) in a 45 × 2.5 cm. glass chromatographic column. The product is washed through the alumina with about 1 l. of ether. The brown eluate is concentrated by distilling the ether through a 45-cm. Vigreux column on a steam bath at atmospheric pressure. When the ether has been distilled, a slight vacuum is applied to remove most of the acetonitrile. When the volume reaches about 50 ml., the mixture is filtered into a 100-ml. distillation flask to free it from some precipitated palladium metal. The flask is rinsed with 10 ml. of ether, and the rinse is combined with the product. The flask is equipped with a 10-cm. Vigreux column for distillation at reduced pressure. After removal of the solvent, 8.1–8.5 g. (55–58%) of 2-methyl-3-phenylpropionaldehyde is collected, b.p. 75–85° (3 mm.) (Note 4),  $n_D^{25}$  1.5113 (Note 5).

## 2. Notes

1. Methallyl alcohol was obtained from Eastman Organic Chemicals.

2. Palladium acetate was purchased from Engelhard Industries.

3. The yield improves slightly with stirring overnight. The checkers obtained the aldehyde in 69% yield in an experiment using stirring overnight.

4. The bulk of the product has b.p. 77–80° (3 mm.).

5. The product is 90–95% pure by gas chromatographic and n.m.r. analyses. The checkers estimated the purity to be at least 95% by these criteria. The n.m.r. spectrum (deuteriochloroform solution, internal tetramethylsilane reference) shows

peaks at 0.95 (doublet,  $J = 6.5$  Hz., 3H), ~2.7 (complex multiplet, 3H), 7.20 (singlet, 5H) and 9.65 p.p.m. (doublet,  $J = 1.5$  Hz., 1H).

## 3. Discussion

The formation of 3-aryl-substituted aldehydes and 3-aryl-substituted ketones by the reaction of "arylpalladium salts" with allylic alcohols is a general reaction.<sup>2</sup> Illustrations of the preparation of two aldehydes and two ketones are given in Table I.

TABLE I  
3-ARYLCARBONYL COMPOUNDS FROM ALLYLIC ALCOHOLS  
AND "PHENYLPALLADIUM ACETATE"<sup>2</sup>

Allylic Alcohol	Product	Yield, %	Boiling Point, °C.
$\text{CH}_2=\text{CHCH}_2\text{OH}$	$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{CHO}$	35	220–225° <sup>a</sup>
<i>trans</i> - $\text{CH}_3\text{CH}=\text{CHCH}_2\text{OH}$	$\text{C}_6\text{H}_5\text{CH}(\text{CH}_3)\text{CH}_2\text{CHO}$	36	67–75° (1 mm.)
<i>trans</i> - $\text{CH}_3\text{CH}=\text{CHCH}(\text{OH})\text{CH}_3$	$\text{C}_6\text{H}_5\text{CH}(\text{CH}_3)\text{CH}_2\text{COCH}_3$	51	70–75° (3 mm.)
$(\text{CH}_3)_2\text{C}=\text{CHCH}(\text{OH})\text{CH}_3$	$\text{C}_6\text{H}_5\text{C}(\text{CH}_3)_2\text{CH}_2\text{COCH}_3$	29	83–87° (2 mm.)

<sup>a</sup> Purification by careful distillation is necessary in this example to remove cinnamaldehyde which is also formed in the reaction (b.p. 252°).

The presence of nitro, carboalkoxy, carboxyl, chloro, formyl, alkyl, and acyl groups does not interfere with the reaction. A single alkoxy group also does not interfere, but if two or more are present, the yields are markedly decreased. The reaction is inhibited by the presence of unhindered, basic nitrogen substituents, by the phenolic group, and probably by the thiol group.

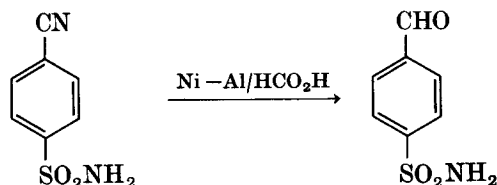
A variation of this procedure involves the use of a catalytic amount of palladium chloride with cupric chloride as a re-oxidant.<sup>2</sup> This method, however, generally gives lower yields and less pure products.

Other preparations of 2-methyl-3-phenylpropionaldehyde include the pyrolysis of a mixture of the calcium salts of 2-methyl-3-phenylpropionic acid and formic acid,<sup>3</sup> and the

pyrolysis of the glycidic ester obtained from phenyl-2-propanone and ethyl chloroacetate.<sup>4</sup>

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# ALDEHYDES FROM AROMATIC NITRILES: *p*-FORMYLBENZENESULFONAMIDE



Submitted by T. VAN ES and B. STASKUN<sup>1</sup>

Checked by A. BROSSI, L. A. DOLAN, and A. LAURENZANO

## 1. Procedure

A 2-l. two-necked round-bottomed flask fitted with a mechanical stirrer and a reflux condenser is charged with 40.0 g. (0.22 mole) of *p*-cyanobenzenesulfonamide (Note 1), 600 ml. of 75% (v/v) formic acid, and 40 g. of Raney nickel alloy (Note 2). The stirred mixture is heated under reflux for 1 hour (Note 3). The mixture is filtered with suction through a Büchner funnel coated with a filter aid (Note 4), and the residue on the funnel is washed with two 160-ml. portions of 95% ethanol. The combined filtrates are evaporated under reduced pressure with a rotary evaporator (Note 5). The solid residue (Note 6) is heated in 400 ml. of boiling water and freed from a small amount of insoluble material by decantation through a plug of glass wool placed in a filter funnel. The filtrate is chilled in an ice bath and the precipitate is collected by filtration with suction, washed with a small amount of cold water and dried at 50°

under vacuum. The crude product weighs about 32 g., m.p. 112–114°.

The crude product is dissolved in 800 ml. of hot 95% ethanol, 15.5 g. of activated carbon (Note 7) is added, and the mixture is swirled periodically while it is allowed to cool for 1 hour. The activated carbon is recovered by filtration with suction through a bed of filter aid (Note 4), the filter cake is washed with 50 ml. of 95% ethanol, and the combined filtrates are evaporated under vacuum with a rotary evaporator. The residue is dissolved in 225 ml. of boiling water, and the hot solution is decanted through glass wool placed in a filter funnel. The filtrate is cooled to 0° and the product is collected by filtration with suction, washed with a small amount of cold water, and dried in a vacuum oven at 50°. The yield of *p*-formylbenzenesulfonamide is 25.6–28.0 g. (62.9–68.8%), m.p. 117–118° (Note 8).

## 2. Notes

1. The checkers used *p*-cyanobenzenesulfonamide purchased from Aldrich Chemical Company, Inc., m.p. 167–169°. The submitters prepared this material according to directions in the literature. The diazotization was conducted according to reference 2 and the cyanation step was performed according to reference 3. The product was crystallized from water, m.p. 152–154°.

2. The checkers used material purchased from Harshaw Chemical Company. The submitters used nickel-aluminum alloy (50% Ni, 50% Al) supplied by British Drug Houses Ltd.

3. The reaction proceeds with some frothing; this is more appreciable and vigorous in mixtures containing a higher proportion of water, for example, when the reduction is conducted in 50% formic acid.<sup>4</sup>

4. Hyflo Supercel, a filter aid purchased from Johns-Manville Corporation, was used by the checkers.

5. This procedure is to be avoided with steam-volatile aldehydes (e.g., *p*-chlorobenzaldehyde) in which case the reduction product is isolated by solvent extraction.<sup>4</sup>

6. The product is contaminated with nickel salts; its infrared spectrum showed little, if any, unchanged nitrile.

7. Norite A, purchased from Matheson Coleman and Bell, was used.

8. The melting point of *p*-formylbenzenesulfonamide has been reported as 118–120°, <sup>4,5</sup> 122°, <sup>6</sup> and 123–124°. <sup>7</sup>

### 3. Discussion

*p*-Formylbenzenesulfonamide has been prepared by chromic acid oxidation of *p*-toluenesulfonamide, <sup>5</sup> the Sommelet reaction on *p*-chloromethylbenzenesulfonamide, <sup>8</sup> and by the Stephen reduction of *p*-cyanobenzenesulfonamide. <sup>5</sup> The present method provides a general procedure for the synthesis of substituted aromatic aldehydes as illustrated in Table I.

TABLE I  
ALDEHYDES FROM AROMATIC NITRILES<sup>a</sup>

Nitrile	Aldehyde	Yield, % <sup>a</sup>
C <sub>6</sub> H <sub>5</sub> CN	C <sub>6</sub> H <sub>5</sub> CHO	97
<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> CN	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> CHO	100
<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CN	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CHO	93
2-C <sub>10</sub> H <sub>7</sub> CN	2-C <sub>10</sub> H <sub>7</sub> CHO	95

<sup>a</sup> Determined as the 2,4-dinitrophenylhydrazone derivative.

Some studies seeking preferred conditions for this reaction have been made. Optimum yields are obtained when the amount of water present is appreciable, and it was noted that the rate of hydrogen evolution increases with increasing water content. A 75% formic acid system appears generally preferred. Under the reaction conditions examined by the submitters, olefins, ketones, esters, amides, and acids are inert, but nitro compounds are reduced to the formamide derivative.

A related method for the synthesis of aldehydes from nitriles has also been studied. <sup>9</sup> This method, which has been found to be extremely effective for the reduction of hindered nitriles to aldehydes, uses moist, preformed Raney nickel catalyst in formic acid. Compounds synthesized by this method are illustrated in Table II.

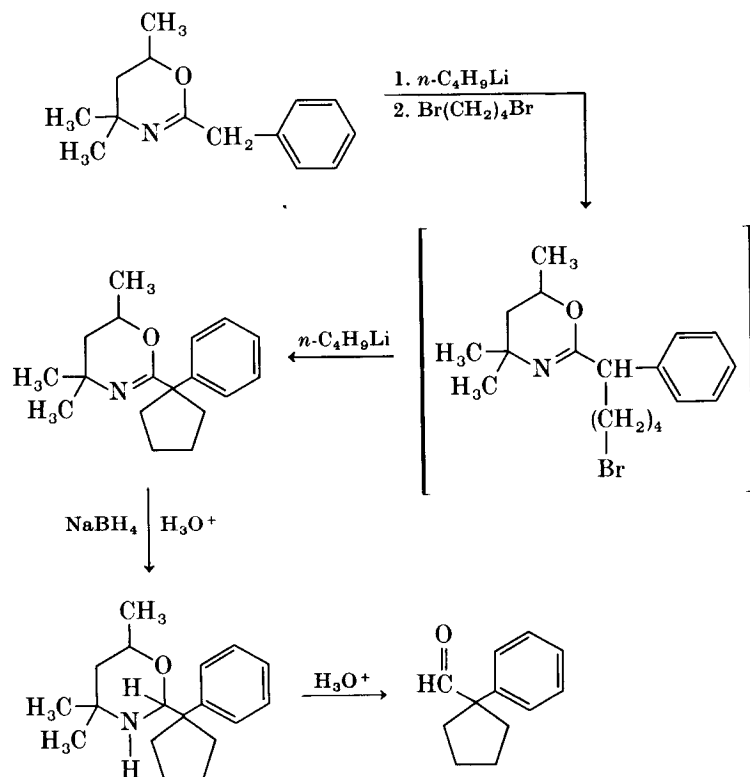
TABLE II  
ALDEHYDES FROM NITRILES WITH RANEY NICKEL CATALYST  
IN FORMIC ACID<sup>9</sup>

Nitrile	Aldehyde	Yield, % <sup>a</sup>
C <sub>6</sub> H <sub>5</sub> CN	C <sub>6</sub> H <sub>5</sub> CHO	72
<i>o</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CN	<i>o</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CHO	65–75
<i>o</i> -ClC <sub>6</sub> H <sub>4</sub> CN	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub> CHO	70–83
<i>o</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CN	<i>o</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CHO	80
2,6-(CH <sub>3</sub> O) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CN	2,6-(CH <sub>3</sub> O) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CHO	60–65
C <sub>6</sub> H <sub>5</sub> CH=CHCN	C <sub>6</sub> H <sub>5</sub> CH=CHCHO	64

<sup>a</sup> Determined as the 2,4-dinitrophenylhydrazone derivative.

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ALDEHYDES FROM 2-BENZYL-4,4,6-TRIMETHYL-5,6-DIHYDRO-1,3(4H)-OXAZINE:  
1-PHENYLCYCLOPENTANECARBOXALDEHYDE



Submitted by IEVA R. POLITZER and A. I. MEYERS<sup>1</sup>  
Checked by DENNIS R. RAYNER and RICHARD E. BENSON

### 1. Procedure

A. 2-(1-Phenylcyclopentyl)-4,4,6-trimethyl-5,6-dihydro-1,3(4H)-oxazine. A 1-l. three-necked flask is equipped with a magnetic stirring bar, a 125-ml. pressure-equalizing funnel fitted with a rubber septum, and a nitrogen inlet tube. The system is flushed with nitrogen and 500 ml. of dry tetrahydrofuran (Note 1), and 21.7 g. (0.100 mole) of 2-benzyl-4,4,6-

trimethyl-5,6-dihydro-1,3(4H)-oxazine (Note 2) are added to the flask. The stirred solution is cooled to  $-78^\circ$  with a dry ice-acetone bath and 49 ml. (0.11 mole) of a 2.25M solution of *n*-butyllithium in *n*-hexane (Note 3) is injected into the addition funnel. The *n*-butyllithium solution is added over a period of 15 minutes, and the funnel is rinsed by injecting 5 ml. of dry tetrahydrofuran. The yellow to orange solution is allowed to stir at  $-78^\circ$  for 30 minutes (Note 4).

1,4-Dibromobutane (23.8 g., 0.11 mole) (Note 5) is injected into the addition funnel and then is added to the solution with stirring over a period of about 15 minutes. The funnel is rinsed by injection of 5 ml. of dry tetrahydrofuran, and the reaction is allowed to stir at  $-78^\circ$  for 45 minutes. *n*-Butyllithium (55 ml., 0.12 mole) in *n*-hexane is injected into the addition funnel and then is added to the solution over a period of 15 minutes. The reaction is stirred at  $-78^\circ$  for 1 hour and then is stored at  $-20^\circ$  overnight (Note 6). The mixture is poured into about 300 ml. of ice water and acidified to pH 2-3 with 9N hydrochloric acid solution. The acidic solution is shaken with three 200-ml. portions of ether, and the ether extracts are discarded. The aqueous layer is made basic by careful addition of 40% sodium hydroxide solution (Note 7). The resulting mixture is shaken with four 200-ml. portions of ether, and the ether extracts are dried over anhydrous potassium carbonate. The ether is removed by distillation using a rotary evaporator to give 24.4–25.8 g. (90–95%) of crude 2-(1-phenylcyclopentyl)-4,4,6-trimethyl-5,6-dihydro-1,3(4H)-oxazine. The product is sufficiently pure for use in the following step.

B. 2-(1-Phenylcyclopentyl)-4,4,6-trimethyltetrahydro-1,3-oxazine. To a 600-ml. beaker containing a magnetic stirring bar are added 200 ml. of tetrahydrofuran, 200 ml. of 95% ethyl alcohol, and 25.0 g. (0.092 mole) of the oxazine obtained in Part A. The mixture is stirred and cooled to  $-35$  to  $-40^\circ$  with an acetone bath to which dry ice is added as needed. A 9N hydrochloric acid solution is added dropwise to the stirred solution until an approximate pH of 7 is obtained as determined by pH paper. A solution of sodium borohydride is prepared by dissolving 5.0 g. (0.13 mole) in a minimum amount of water

(5–8 ml.) to which 1 drop of a 40% solution of sodium hydroxide is added (Note 8). The sodium borohydride solution and 9*N* hydrochloric acid solution are alternately added dropwise to the stirred solution so that a pH 6–8 is maintained (Note 9). During the addition care is taken to maintain a temperature between –35 and –45°. After addition of the borohydride solution is complete, the solution is stirred at –35° for 1 hour. A pH of 7 is maintained by occasional addition of a 9*N* hydrochloric acid solution (Note 10). The reaction mixture is then stored at –20° overnight.

The reaction mixture is poured into 300 ml. of water, and the resulting mixture is made basic with 40% sodium hydroxide solution. The mixture is shaken three times with 200-ml. portions of ether, and the combined ether extracts are washed with 10 ml. of a saturated sodium chloride solution. After drying over potassium carbonate, the ether is removed by distillation with a rotary evaporator. The product weighs 22.9–25.0 g. (91–99%) and is used without purification in the next step (Note 11).

C. *1-Phenylcyclopentanecarboxaldehyde*. The crude tetrahydrooxazine (25.0 g., 0.092 mole) from Part B is heated at reflux with 300 ml. of water containing 37.8 g. (0.300 mole) of oxalic acid dihydrate for 3 hours. The solution is cooled, and the aldehyde is extracted with four 150-ml. portions of petroleum ether (b.p. 40–60°). The organic extracts are combined and washed with 10 ml. of saturated sodium bicarbonate solution and dried with anhydrous powdered magnesium sulfate. The petroleum ether is removed by distillation with a rotary evaporator, and the product is distilled through a Vigreux column to give 7.8–8.7 g. (50–55%) of 1-phenylcyclopentanecarboxaldehyde, b.p. 70–73° (0.1 mm.)  $n_{D}^{26}$  1.5350, infrared spectrum (neat) 1720  $\text{cm}^{-1}$  (C=O) (Note 12).

## 2. Notes

1. Tetrahydrofuran is dried by distillation from lithium aluminum hydride. (See *Org. Syn.*, **46**, 105 (1966) for warning note regarding the purification of tetrahydrofuran.)

2. 2-Benzyl-4,4,6-trimethyl-5,6-dihydro-1,3(4*H*)-oxazine is available from Columbia Organic Chemicals Company, Inc. The product was distilled, b.p. 80–82° (0.25 mm.). It may be prepared according to a modification of the method of Ritter and Tillmanns.<sup>2</sup> To a 2-l. flask, equipped with a thermometer, a stirrer, and a 250-ml. addition funnel is added 200 ml. of concentrated sulfuric acid (95–98%). Stirring is begun, the acid is cooled to 0–5° with an ice bath, and 128.7 g. (1.1 mole) phenylacetonitrile is added from the funnel at such a rate that the temperature is maintained at 0–5°. After the addition is complete, 118 g. (1.0 mole) of 2-methyl-2,4-pentanediol is added at a rate to maintain a temperature of 0–5° in the reaction vessel. The mixture is stirred for an additional hour and then poured onto 700 g. of crushed ice. The aqueous solution is washed with two 75-ml. portions of chloroform, and the extracts discarded. The aqueous solution is made alkaline with 40% sodium hydroxide solution with ice being added periodically during the neutralization to keep the solution temperature below 35°. The yellow oil is separated, and the aqueous solution is washed three times with 75-ml. portions of ether. The oil and ether extracts are combined, and the solution is dried over anhydrous potassium carbonate. The ether is removed by distillation using a rotary evaporator, and the product is distilled through a 25-cm. Vigreux column to yield 107–115 g. (49–53%) of 2-benzyl-4,4,6-trimethyl-5,6-dihydro-1,3(4*H*)-oxazine as a straw-yellow liquid, b.p. 78–80° (0.25 mm.);  $n_{D}^{27}$  1.5085; infrared spectrum (neat) 1660 and 1600  $\text{cm}^{-1}$ , n.m.r. (deuteriochloroform solvent, internal tetramethylsilane reference) 1.08 (singlet, 6H), 3.32 (singlet, 2H), 4.04 (multiplet, 1H) and 7.08 p.p.m. (multiplet, 5H).

3. *n*-Butyllithium in *n*-hexane is available from Lithium Corporation of America, Inc.

4. If less solvent is used, the anion may appear as a yellow precipitate, but it is also usable in this form.

5. 1,4-Dibromobutane was distilled, b.p. 40–45° (0.5 mm.).

6. Alternatively, the reaction mixture may be allowed to reach room temperature over a period of 2–3 hours.

7. Ice may be added to keep the mixture cool during the neutralization.

8. The aqueous borohydride suspension is warmed, and the borohydride lumps crushed to achieve a homogeneous solution. The product available from Alfa Inorganics, Inc. was used by the checkers.

9. It is convenient to introduce the acid and hydride solutions from two burets or dropping funnels placed above the beaker. A total volume of about 15 ml. of 9*N* hydrochloric acid solution is required.

10. The reaction can be conveniently monitored by i.r. absorption spectroscopy by observing the intensity of the band at  $1650\text{ cm}^{-1}$  ( $\text{C}=\text{N}$ ). The submitters observed almost complete disappearance of this band whereas the checkers found it still present in medium intensity in their product. In those instances where the  $\alpha$ -carbon bears three alkyl substituents, steric effects retard the rate of addition, and in some cases (i.e.,  $\alpha,\alpha,\alpha$ -triethyl or larger groups) the  $\text{C}=\text{N}$  bond is resistant to reduction.

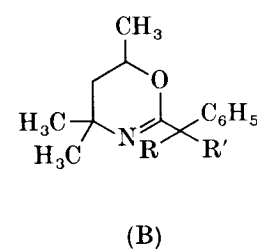
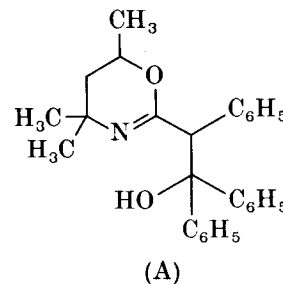
11. The intensity of the infrared band at  $1650\text{ cm}^{-1}$  should be weak.

12. The n.m.r. spectrum (carbon tetrachloride solution, internal tetramethylsilane reference) shows peaks at 9.3 (singlet, 1H, CHO), 7.2 (singlet, 5H, phenyl), and 1.5–2.7 p.p.m. (multiplet, 8H,  $-(\text{CH}_2)_4-$ ). Gas chromatography on a  $240\text{ cm.} \times 6\text{ mm.}$  column packed with 10% SE-30 on Chromosorb P at  $120^\circ$  gives a single peak with a retention time of 1.3 minutes.

### 3. Discussion

This procedure illustrates a general method for preparing  $\alpha$ -phenyl aldehydes.<sup>3</sup> Additional examples are given in Table I.

A limitation to this reaction sequence is that the reduction of the dihydrooxazine fails if bulky substituents are present. Thus the alkylated oxazines A and B were not reduced under the reaction conditions specified in this procedure.



B	
R	R'
Et	Et
<i>n</i> -Pr	<i>n</i> -Pr
<i>n</i> -Bu	<i>n</i> -Bu
Et	<i>n</i> -Bu

TABLE I  
ALDEHYDES FROM 2-BENZYL-4,4,6-TRIMETHYL-5,6-DIHYDRO-1,3(4H)-  
OXAZINE<sup>4-7</sup>

Alkylating Agent	Aldehyde	Yield, %
$\text{CH}_3\text{I}$	$\text{C}_6\text{H}_5\text{CHCHO}$   $\text{CH}_3$ $\text{CH}_3$	65
$\text{CH}_3\text{I}$ (2.0 equiv.)	$\text{C}_6\text{H}_5\text{C}-\text{CHO}$   $\text{CH}_3$	48
$\text{CH}_3\text{CH}_2\text{CH}_2\text{Br}$	$\text{C}_6\text{H}_5\text{CHCHO}$   $\text{CH}_2\text{CH}_2\text{CH}_3$	64
$\text{CH}_2=\text{CHCH}_2\text{Br}$	$\text{C}_6\text{H}_5\text{CHCDO}$   $\text{CH}_2\text{CH}=\text{CH}_2$	70*
$\text{BrCH}_2\text{CH}_2\text{Br}$	$\text{C}_6\text{H}_5-\text{CHO}$   	57
$\text{Br}(\text{CH}_2)_3\text{Br}$	$\text{C}_6\text{H}_5-\text{CHO}$   	49
	$\text{C}_6\text{H}_5-\text{C}-\text{CHO}$    	54
	$\text{C}_6\text{H}_5-\text{C}-\text{CHO}$    $\text{C}_6\text{H}_5-\text{CH}$	63

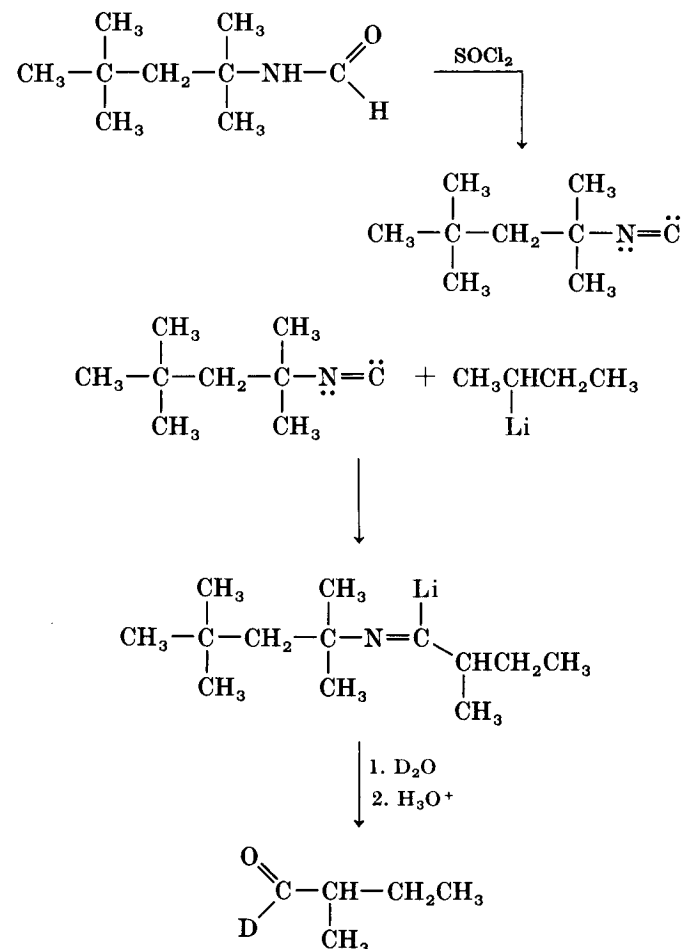
\* Reduction was performed with  $\text{NaBD}_4$ .

This technique may also be modified to prepare acetaldehyde derivatives by use of 2,4,4,6-tetramethyl-5,6-dihydro-1,3(4H)-oxazine<sup>3-7</sup> and 2-carboethoxy acetaldehydes using 2-(carboethoxymethyl)-4,4,6-trimethyl-5,6-dihydro-1,3(4H)-oxazine.<sup>3</sup> Functionalized aldehydes and dialdehydes may also be obtained by suitable modification.<sup>8</sup> Generally, the intermediates can be used without purification and the overall yields of the aldehydes range from 50–70%.

In addition to the present method, 1-phenylcyclopentanecarboxaldehyde has been prepared by the reduction of N-acylaziridines obtained from 1-phenylcyclopentanecarboxylic acid.<sup>9</sup>

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# 1-d-ALDEHYDES FROM ORGANOMETALLIC REAGENTS: 1-d-2-METHYLBUTANAL



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Checked by FRANK E. HERKES and RICHARD E. BENSON

## 1. Procedure

A. 1,1,3,3-Tetramethylbutyl isonitrile. A 3-l. three-necked round-bottomed flask is fitted with a Hershberg stirrer, a 500-ml. pressure-equalizing addition funnel, and a nitrogen gas



inlet tube. The glassware is flamed dry under a nitrogen atmosphere, and the flask allowed to cool. The nitrogen inlet tube is replaced by a low-temperature thermometer, and the nitrogen line is attached to a Y-tube placed on the addition funnel. To the flask are added 118 g. (0.75 mole) of *N*-(1,1,3,3-tetramethylbutyl)-formamide (Note 1) and 1500 ml. of dimethylformamide (Note 2). The addition funnel is charged with a premixed (Note 3) solution consisting of 89 g. (55 ml., 0.75 mole) of thionyl chloride and 250 ml. of dimethylformamide. The flask is immersed in a dry ice-acetone bath, and moderately fast stirring is commenced. When the temperature of the flask reaches  $-50^{\circ}$ , the solution in the funnel is added at a rate such that the temperature ranges between  $-55^{\circ}$  and  $-50^{\circ}$  (about 10 minutes are required for the addition). After the addition is complete, the bath is removed momentarily to allow the reaction temperature to rise to  $-35^{\circ}$ . The bath is then replaced, and 159 g. (1.50 mole) of dry sodium carbonate (Note 4) is added directly to the mixture (Note 5). After the addition the bath is removed and the flask contents are stirred for an additional 6 hours at room temperature (Note 6). The reaction mixture (Note 7) is poured into a 6-l. Erlenmeyer flask containing 3 l. of ice water (Note 8). The reaction flask is rinsed with 300 ml. of pentane and sufficient water to dissolve the inorganic material that may be present (Note 9). The washings are added to the Erlenmeyer flask. The mixture is stirred vigorously for 5 minutes, and the layers are separated. The upper layer is washed twice with 100-ml. portions of water and then is dried over anhydrous sodium sulfate. The solution is filtered and the pentane is removed by distillation. The crude tetramethylbutyl isonitrile is distilled through a  $1.5 \times 15$  cm. Vigreux column. The fraction having b.p.  $55.5\text{--}56.5^{\circ}$  (11 mm.) is collected,  $n_{D}^{25}$  1.4178,  $d_{25}^{25}$  0.7944. The yield is 86–90 g. (82–87%). The compound shows strong absorption in the infrared at  $2130\text{ cm.}^{-1}$  attributable to the isonitrile function (carbon tetrachloride solution). The n.m.r. spectrum (neat, external tetramethylsilane reference) shows peaks at 1.08 (singlet, 9H,  $\text{C}(\text{CH}_3)_3$ ), 1.43 (triplet,  $J_{14\text{N-H}} = 2\text{ Hz.}$ , 6H,  $\text{C}(\text{CH}_3)_2$ ), and 1.58 p.p.m. (triplet,  $J_{14\text{N-H}} = 2.3\text{ Hz.}$ , 2H,  $\text{CH}_2$ ).

B. *N*-(1-*d*-2-Methylbutylidene)-1,1,3,3-tetramethylbutylamine. (Note 10). A 1-l. three-necked round-bottomed flask is fitted with a Teflon paddle stirrer, a 500-ml. pressure-equalizing addition funnel, and a nitrogen gas inlet tube. The glassware is flamed dry under a nitrogen atmosphere and allowed to cool. The nitrogen inlet tube is replaced by a thermometer, and the nitrogen line is attached to a Y-tube placed on the addition funnel. A solution of 27.8 g. (35.1 ml., 0.2 mole) of 1,1,3,3-tetramethylbutyl isonitrile in 300 ml. of anhydrous ether is added to the flask. The flask is cooled to  $0^{\circ}$  by means of an ice-salt bath, and 0.2 mole of *sec*-butyllithium in hexane (Note 11) is transferred to the addition funnel by means of a syringe. The alkyllithium solution is added to the stirred (Note 12) solution at such a rate that the temperature never exceeds  $5^{\circ}$ . After the addition is complete, the mixture is stirred for 15 minutes as the temperature slowly drops to  $-5^{\circ}$ , and 8 ml. (0.4 mole) of deuterium oxide (Note 13) is then injected rapidly into the reaction mixture (Note 14). The ice bath is removed; the mixture is stirred for 30 minutes and then is filtered through a Büchner funnel into a 1-l. round-bottomed flask. The reaction flask is rinsed with pentane, and the rinse is added to the flask. After evaporation of the solvent, 33.7–34.9 g. (85–88%) of the aldimine is collected by distillation through a  $1.5 \times 15$  cm. Vigreux column, b.p.  $52.5\text{--}54^{\circ}$  (1.5 mm.),  $n_{D}^{24.5}$  1.4321. The infrared spectrum (neat) shows strong absorption at  $1663\text{ cm.}^{-1}$  ( $\text{C}=\text{N}$ ).

C. 1-*d*-2-Methylbutanal. A 1-l. three-necked round-bottomed flask is equipped with a dropping funnel, a gas inlet tube for steam, and a Dean-Stark trap to which is attached a condenser through which acetone cooled to  $-15^{\circ}$  is circulated (Note 15). A solution of 50.4 g. (0.40 mole) of oxalic acid dihydrate in 200 ml. of water is added to the flask, and the solution is heated at reflux. Steam is introduced into the flask, and when some begins to condense in the Dean-Stark trap, the distilled aldimine from part B is added dropwise from the funnel. The aldehyde and water collect in the trap, and the water layer is periodically removed. After the distillation of the aldehyde is complete, the product is drained from the trap, and the water layer is separated

and discarded. The oil is washed with three 25-ml. portions of a saturated sodium chloride solution and then dried over anhydrous calcium sulfate. The crude aldehyde is decanted from the drying agent and distilled through a short Vigreux column to give 13.0–13.3 g. (87–88%) of high-quality 1-*d*-2-methylbutanal, b.p. 92–93°,  $n_{D}^{30}$  1.3896 (Note 16). The infrared spectrum (neat) shows strong adsorption at 1721  $\text{cm}^{-1}$  attributable to the carbonyl function.

## 2. Notes

1. N-(1,1,3,3-tetramethylbutyl)-formamide is prepared in 86–90% yield by refluxing 194 g. (1.5 moles) of 1,1,3,3-tetramethylbutylamine with 138 g. (3.0 moles) of formic acid in 400 ml. of toluene. Azeotropic distillation using a Dean-Stark trap gradually removes all water and excess formic acid. The toluene is removed by distillation at atmospheric pressure, and the product is distilled at reduced pressure, b.p. 76–77° (1 mm.),  $n_{D}^{25}$  1.4521. The yield is 203–214 g. (86–90%).

2. Industrial grade dimethylformamide is purified by distillation, first at atmospheric pressure to remove most of the water in the initial small fraction, and then by distillation at reduced pressure from barium oxide, b.p. 63° (30 mm.).

3. A temperature rise of about 30° is observed.

4. Commercial anhydrous sodium carbonate is dried in a vacuum oven at 130° for 1 hour.

5. The checkers used a solid addition funnel and added the sodium carbonate under nitrogen over a 10-minute period.

6. The mixture can be left stirring overnight since the isonitrile is stable to the reaction conditions. Alternatively, a hot water bath can be used, with very fast stirring, to heat the mixture quickly to 35°. The bath is then removed, and after 1 hour of additional stirring, the mixture is ready for the workup procedure.

7. *Isonitriles are presumed to be toxic*, and it is recommended that the workup procedure be performed in a hood. Unlike most isonitriles, however, 1,1,3,3-tetramethylbutyl isonitrile is not malodorous. It has a sweetish pine odor, which becomes unpleasant only after continued inhalation.

8. The addition of the reaction mixture to water is exothermic.

9. The inorganic salts are not always soluble in the amount of water specified.

10. This procedure uses the commercially available *sec*-butyllithium reagent. The submitters state that the corresponding Grignard reagent may also be used. A 300-ml. three-necked round-bottomed flask is fitted with an addition funnel, a reflux condenser, a magnetic stirring bar, and a nitrogen inlet tube. Magnesium turnings (3.65 g., 0.15 mole) and 80 ml. of anhydrous tetrahydrofuran (Note 17) are added to the flask, and a nitrogen atmosphere is maintained. 2-Bromobutane (20.6 g., 0.15 mole), 0.25 ml. of ethylene bromide, and 70 ml. of tetrahydrofuran are placed in the addition funnel. Stirring is begun, and the solution from the funnel is added dropwise at a rate which sustains refluxing. After the addition is complete, the solution is stirred until room temperature is reached. The amount of Grignard reagent prepared is determined (Note 18). To this Grignard solution is added 14.2 g. (0.102 mole) of 1,1,3,3-tetramethylbutyl isonitrile (Note 19). After stirring for 4–6 hours (Note 20), the solution is cooled in an ice bath to 0°. To the rapidly stirred solution (Note 21) is injected 6.0 ml. (0.30 mole) of deuterium oxide (Note 13). The ice bath is removed, and the mixture is stirred for 10 minutes, and then 50 ml. of water is added (Note 22). The contents of the reaction flask are decanted into a 1-l. separatory funnel containing 200 ml. of ether. The aqueous layer is separated, and the ether layer is washed with 100 ml. of saturated sodium chloride solution. The magnesium salts remaining in the reaction vessel are washed twice with 100-ml. portions of ether. The ether extracts are washed with 100 ml. of saturated sodium chloride solution. The ether solutions are combined and dried over anhydrous sodium sulfate. The solvent is evaporated with a rotary evaporator to give the crude aldimine. Distillation (see Part B) yields 13.7 g. (67%) of the pure aldimine. Hydrolysis and steam distillation (as described in Note 15) yield 5.85 g. of the aldehyde in an overall yield of 65% (Note 23).

11. The commercially available organolithium reagent is titrated with benzoic acid using triphenylmethane as an indi-

cator according to the procedure of Eppley and Dixon.<sup>2</sup> The checkers used product available from Alfa Inorganics, Inc.

12. During the addition of the alkylolithium the mixture becomes gelatinous. As this happens, the stirring rate is increased to ensure thorough mixing.

13. Deuterium oxide having an isotopic purity of >99% was used. The product available from Columbia Organic Chemicals Company, Inc., was used by the checkers.

14. The stirring should be very rapid at this point or frothing will occur. The flask temperature will reach 30° during deuterio-lysis. It is important that the temperature of the ice-salt bath remains at -10° to -15°.

15. The submitters recommend the following procedure for steam distillation of low-boiling aldehydes. A 500-ml. three-necked flask is fitted with two addition funnels, one of which has a double-bore stopcock for external drainage. This addition funnel is fitted with a cold finger (-5°) and an inlet tube leading to a bubbler and a nitrogen source. Into the other addition funnel is placed the aldimine. While the aldimine is added dropwise to the refluxing oxalic acid solution, the distillate passes up the equalizing pressure tube of the collecting funnel and is condensed by the cold finger. The water layer is periodically drained back into the flask. After distillation, the aldehyde is washed with saturated sodium chloride solution. It is then drained from the funnel through the external tube.

16. The submitters found that analysis of the undistilled aldehyde by gas chromatography indicated a purity of 98.6%. The analysis was conducted on a column packed with 16% LS-40 on Chromosorb P/AW at 100°. N.m.r. analysis indicated an isotopic purity of 97.9% (trace of impurity at 9.60 p.p.m. due to CHO, carbon tetrachloride solution, internal tetramethylsilane as reference). If the crude aldimine is hydrolyzed, the aldehyde is obtained in 96% overall yield; however, the purity is only 94% by gas chromatography analysis. The checkers found no detectable impurity by gas chromatography in the distilled aldehyde, and the n.m.r. spectrum indicated very high isotopic purity.

17. Alkyl magnesium halides form intermediates with

tetramethylbutyl isonitrile which are not very soluble in ether. If it is necessary to prepare the Grignard reagent in ether, the ether should either be diluted with tetrahydrofuran or replaced by tetrahydrofuran. See the warning note in *Org. Syn.*, **46**, 105 (1966) for purification of tetrahydrofuran.

18. The molarity is determined<sup>3</sup> by adding an excess of standardized acid and back-titrating with base. The moles of Grignard reagent present are then determined based on a volume of 150 ml. When ether is used to prepare the Grignard reagent, an actual measurement of the volume is necessary. This can be done conveniently by transferring the solution back into the addition funnel with a large graduated syringe. The Grignard reagent content averages 0.102 mole.

19. The molar amount of 1,1,3,3-tetramethylbutyl isonitrile used is equivalent to the Grignard reagent content.

20. After 4 hours, periodic aliquots are taken and worked up. The disappearance of the isonitrile absorption at 2130 cm.<sup>-1</sup> and the appearance of the imine absorption at 1665 cm.<sup>-1</sup> are used for analysis. Usually within 6 hours the isonitrile peak vanishes or remains at a very low constant intensity indicative of completion of the reaction.

21. The sudden quenching with deuterium oxide minimizes the exchange between the 1-metalloalimine and the active hydrogen at the C-2 position of the already-deuteriated aldimine. Performing the reaction in refluxing tetrahydrofuran produces an exchange (approximately 10%) with incorporation of deuterium in the C-2 position. If only the 1-H-aldehyde is desired, 50 ml. of water is added dropwise.

22. Saturated ammonium chloride solution slowly hydrolyzes the aldimine to the aldehyde, which, in this case, is undesirable.

23. The n.m.r. analysis shows that deuterium incorporation at the C-1 position is 95.3% and at C-2, 5%.

### 3. Discussion

This reaction illustrates a general procedure for the preparation of 1-*d*-aldehydes from aliphatic and alicyclic<sup>4</sup> Grignard<sup>5</sup> and lithium<sup>6</sup> reagents. The use of the lithium reagent is normally preferred because of higher yields and greater isotopic purity

if the 1-*d*-aldehyde is desired. For the synthesis of aromatic aldehydes, the use of the lithium reagent is specifically preferred since aromatic Grignard reagents react poorly with 1,1,3,3-tetramethylbutyl isonitrile. The aldehydes prepared by this method are illustrated in Table I.

TABLE I  
ALDEHYDES FROM 1,1,3,3-TETRAMETHYLBUTYL ISONITRILE  
AND ORGANOMETALLIC REAGENTS

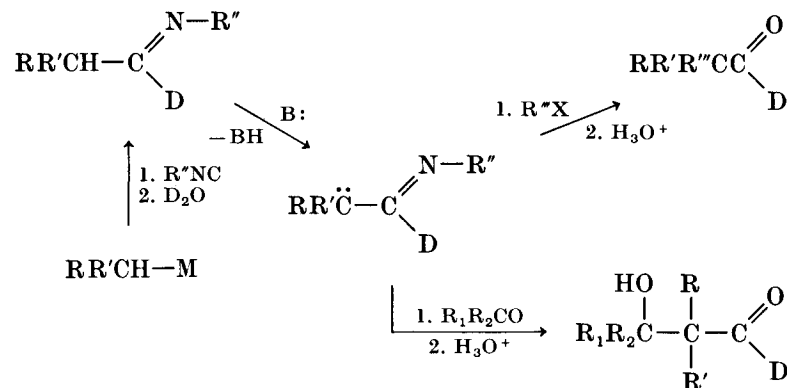
Organometallic Reagent	Aldehyde, % Yield
<i>n</i> -Butyllithium	93 <sup>a</sup>
Phenyllithium	55 <sup>a</sup>
<i>sec</i> -Butylmagnesium bromide	67 (96 <sup>b,c</sup> )
<i>t</i> -Butylmagnesium bromide	48 <sup>b</sup>
<i>n</i> -Hexylmagnesium bromide	62 <sup>b</sup>
2-Phenylethylmagnesium bromide	63 (80 <sup>b,c</sup> )
Cyclopentylmagnesium bromide	66 (89 <sup>b,c</sup> )

<sup>a</sup> Reference 6.

<sup>b</sup> Reference 5.

<sup>c</sup> Percent deuterium at C-1 as determined by n.m.r.

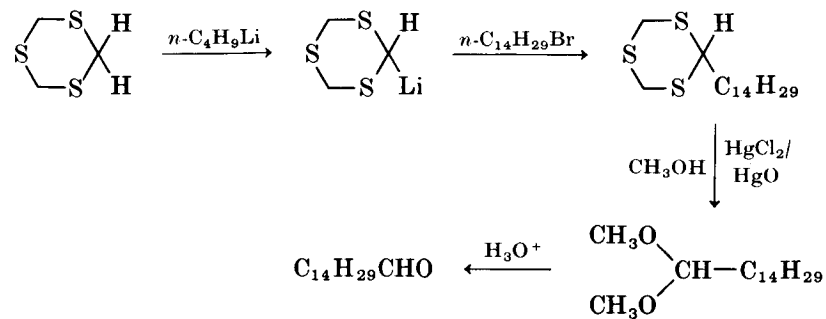
The intermediate aldimines can also be alkylated<sup>7</sup> or used as condensing agents<sup>8</sup> by removal of the  $\alpha$ -hydrogen atom. The metalloaldimine is a useful intermediate for the preparation



of  $\alpha$ -keto acids, acyloins,  $\beta$ -hydroxy ketones, and silyl ketones.<sup>5,6</sup>

1. Chemistry Department, Florida State University, Tallahassee, Florida 32306.
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# ALDEHYDES FROM *sym*-TRITHIANE: *n*-PENTADECANAL



Submitted by D. SEEBACH and A. K. BECK<sup>1</sup>

Checked by A. BROSSI, N. W. GILMAN, and G. WALSH

## 1. Procedure

A. 2-Tetradecyl-*sym*-trithiane. In a 1-l. round-bottomed flask with a side arm and containing a magnetic stirring bar is placed 25.0 g. (0.180 mole) of finely ground, pure *sym*-trithiane (Note 1). The flask is equipped with a three-way stopcock and a rubber septum on the side arm. The air in the flask is replaced by dry nitrogen (Note 2). Tetrahydrofuran (Note 3) (350 ml.) is added by syringe, and the resulting slurry is stirred vigorously

in a cooling bath at  $-30^{\circ}$  (Note 4). After the addition of 0.190 mole of *n*-butyllithium (1.5–2.5 molar in *n*-hexane) (Note 5), the mixture is stirred for 1.5–2.5 hours, keeping the bath temperature between  $-25^{\circ}$  and  $-15^{\circ}$ . After this period of time the trithiane is dissolved (Note 6), and dry ice is added (no excess!) to the bath until the temperature is about  $-70^{\circ}$ . To this cooled solution is rapidly added 50.0 g. (49.5 ml., 0.180 mole) of 1-bromotetradecane (myristyl bromide) (Note 7) by syringe, and the resulting mixture is stirred overnight, during which time the bath temperature rises to  $0$ – $25^{\circ}$ , and a heavy colorless precipitate separates. Stirring is continued for 1 hour at room temperature, and the mixture is then poured into a 2-l. separatory funnel containing 800 ml. of water and 500 ml. of carbon tetrachloride. After shaking, the layers are separated and the aqueous layer is shaken with two additional 500-ml. portions of carbon tetrachloride. Some undissolved trithiane is filtered from the combined organic layers, which are then washed with water, dried over anhydrous potassium carbonate, and the solvent removed by evaporation to yield 54–59 g. of crude solid 2-tetradecyl-*sym*-trithiane after drying under reduced pressure (Note 8).

B. *Pentadecanal dimethyl acetal*. The crude material obtained from Part A is placed into a 2-l. three-necked flask fitted with an overhead stirrer, a reflux condenser with drying tube, and a stopper. Methanol (1 l.) (reagent grade) is added, the stirrer is started, and 40 g. (0.185 mole) of mercuric oxide and 100 g. (0.368 mole) of mercuric chloride are introduced. The mixture is heated under reflux for 4.5 hours and filtered through a Büchner funnel after cooling. The residue is washed with 300 ml. of pentane (Note 9), and the methanol and pentane filtrates are combined and poured into 1 l. of water. The layers are separated and the lower aqueous layer is shaken with two 500-ml. portions of pentane. The combined organic layers are quickly washed with 10% ammonium acetate solution (Note 10) and with water. The solution is dried over sodium sulfate, and the pentane is evaporated under reduced pressure to give 30.0–32.5 g. of the crude acetal as a mobile, slightly yellow oil.

C. *n*-Pentadecanal. The crude acetal from Part B is dissolved

in 600 ml. of tetrahydrofuran and 150 ml. of water containing 2 g. of *p*-toluenesulfonic acid monohydrate is added. The resulting pale mixture is heated at reflux for 1 hour and cooled. The hydrolysate is poured into 600 ml. of water and extracted with three 300-ml. portions of pentane (Note 9). The colorless pentane extracts are combined, washed three times with saturated sodium bicarbonate solution and once with water, and dried over sodium sulfate. Evaporation of the solvent furnishes an oil which upon distillation under reduced pressure (Note 11) yields 18.7–22.5 g. of *n*-pentadecanal, b.p.  $103$ – $106^{\circ}$  (0.2 mm.). The overall yield from 1-bromotetradecane is 47–55%. The product solidifies eventually and should be kept under an inert atmosphere in the refrigerator.

## 2. Notes

1. It is essential that the *sym*-trithiane be of good purity. Commercial *sym*-trithiane can be purified by extraction from a thimble in a hot extractor using 300 ml. of toluene for 30 g. of trithiane. After cooling the extract to  $0^{\circ}$ , *sym*-trithiane is recovered by filtration and recrystallized from toluene. In one run the checkers used *sym*-trithiane as obtained from Eastman Organic Chemicals and observed a 10% decrease in yield of *n*-pentadecanal.

2. This is done by evaporating and filling with dry nitrogen three times; during the reaction a pressure of about 50 mm. is maintained against the atmosphere using a mercury bubbler.

3. Tetrahydrofuran is distilled from a blue solution of benzophenone ketyl obtained by refluxing tetrahydrofuran in the presence of sodium wire, some potassium, and benzophenone. See *Org. Syn.*, **46**, 105 (1966) for a warning note regarding the purification of tetrahydrofuran.

4. A 2-l. Dewar cylinder was used.

5. The checkers used 120 ml. of 1.6*M* *n*-butyllithium in hexane, obtained from Foote Mineral Company.

6. If the trithiane, apart from a few crystals, does not dissolve entirely, the workup procedure is complicated. The crude tetradecyltrithiane must then be purified (by dissolving in

500 ml. of carbon tetrachloride at 30°, filtering, and precipitating with 1.5 l. of methanol) before conversion to the acetal.

7. Commercial product (Aldrich Chemical Company, Inc., or Matheson Coleman and Bell) proved satisfactory without further purification. The purity should be checked by refractive index and/or gas chromatography.

8. The crude tetradecyltrithiane contains 4–6% of *sym*-trithiane and melts at 69–71°, recrystallization (Note 6) gives pure product, m.p. 76.3–76.6°.

9. Low-boiling ligroin can be used as well.

10. A white precipitate is formed during the first and second washing.

11. A short path distillation apparatus with a cold finger but no condenser should be used since the product may crystallize. The distillation is carried out under nitrogen or argon (balloon at capillary).

### 3. Discussion

The procedure described here provides a convenient route to aldehydes with trithiane serving as an inexpensive, "masked" carbonyl group.<sup>2–4</sup> The reaction is limited, however, to the use of primary alkyl halides, aldehydes, and ketones for elaboration of the carbon chain through attack on the metallated trithiane. Examples of aldehydes synthesized by this method are given in Table I.

The S-acetal is converted to the O-acetal in anhydrous methanol because hydrolysis of monosubstituted trithianes in aqueous methanol furnishes a mixture of the free aldehyde and its O-acetal derivative. It is advantageous to store aldehydes as the O-acetal derivatives since free aldehydes are susceptible to polymerization and oxidation.

This method has several common features with the dithiane method<sup>5</sup> that is useful for the synthesis of aldehydes and ketones.<sup>4</sup> This latter method is illustrated by the synthesis of cyclobutanone (page 76).

*n*-Pentadecanal has also been prepared by pyrolysis of  $\alpha$ -hydroxy-<sup>6</sup> and  $\alpha$ -methoxypalmitic acid,<sup>7</sup> from  $\alpha$ -bromo-

palmitic acid chloride and sodium azide,<sup>8</sup> and from  $\alpha$ -hydroxypalmitic acid and lead tetraacetate.<sup>9</sup>

TABLE I  
ALDEHYDES FROM 2-LITHIO-1,3,5-TRITHIANE AND ALKYL HALIDES

Halide	2-Alkyl-1,3,5-Trithiane Yield, % <sup>a,b,c</sup>	Aldehyde Dimethyl Acetal Yield, % <sup>a,b</sup>	Aldehyde	
			Product	Yield, % <sup>a,e,f</sup>
1-Bromopentane	96	66 <sup>d</sup>	<i>n</i> -Hexanal	43
(S)-(+)-1-Iodo-2-methylbutane	98	67 <sup>d,e</sup>	(S)-(-)-3-Methylpentanal	41
1-Bromoheptane	100	60 <sup>d</sup>	<i>n</i> -Octanal	45
1-Bromodecane	100	99 <sup>c</sup>	<i>n</i> -Undecanal	65
1-Bromohexadecane	100	60 <sup>c</sup>	<i>n</i> -Heptadecanal	32
Benzyl Bromide	100	32 <sup>d</sup>	Phenylacetaldehyde	20

<sup>a</sup> Based on halide.

<sup>b</sup> Reaction conducted on 100 mmoles scale.

<sup>c</sup> Crude product.

<sup>d</sup> Distilled product.

<sup>e</sup> Reaction conducted on 5–10 mmoles scale.

<sup>f</sup> Yield of distilled or recrystallized product.

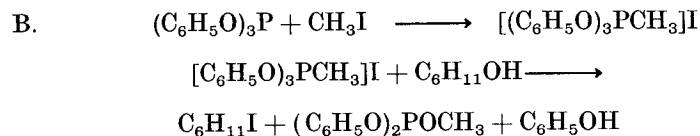
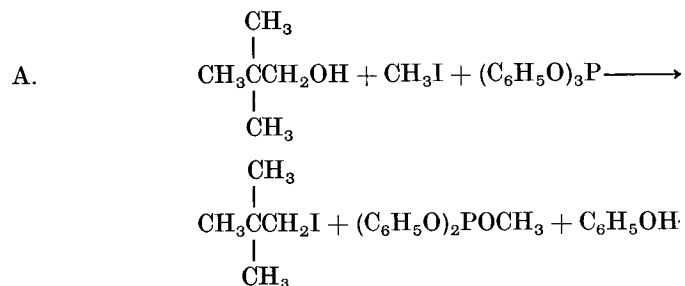
<sup>g</sup> (+)-Iodide with optical purity of 89% gave acetal with  $\alpha_D + 7.6^\circ$  (neat,  $l = 100$  mm.).

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## ALKYL IODIDES

## A. Neopentyl iodide

## B. Iodocyclohexane

Submitted by H. N. RYDON<sup>1</sup>

Checked by W. FUHRER, R. KEESE, and A. ESCHENMOSER

*Note.* Two procedures are given. Procedure A is the simplest to perform, but B is preferred for sensitive alcohols and in cases where elimination to give olefins is expected, for example, with all tertiary and many secondary alcohols. Procedure A is best for sterically hindered alcohols, for example, neopentyl alcohol.

## 1. Procedures

A. *Neopentyl iodide.* A 500-ml. two-necked round-bottomed flask is fitted with a reflux condenser to which is attached a calcium chloride drying tube. One hundred thirty-six grams (115 ml., 0.44 mole) of triphenyl phosphite, 35.2 g. (0.4 mole) of neopentyl alcohol, and 85 g. (37 ml., 0.60 mole) of methyl iodide (Note 1) are added to the flask, and a thermometer is inserted that is of sufficient length to extend into the liquid contents of the flask. The mixture is heated under gentle reflux

by means of an electric heating mantle until the temperature of the refluxing liquid rises from its initial value of 75–80° to about 130°, and the mixture darkens and begins to fume. The time required is about 24 hours. It is necessary to adjust the heat input from the mantle from time to time as the reaction proceeds and the rate of refluxing diminishes (Note 2).

The reaction mixture is distilled under reduced pressure through a 13-cm. Vigreux column. The fraction boiling below 65° (50 mm.) is collected, washed with 50 ml. of water and then with 50-ml. portions of cold 1N sodium hydroxide solution until the washings no longer contain phenol (Note 3). The product is washed again with 50 ml. of water, dried over calcium chloride and redistilled. There is obtained 51–60 g. (64–75%) of neopentyl iodide, b.p. 54–55° (55 mm.),  $n_D^{21}$  1.4882 (Note 4).

B. *Iodocyclohexane.* A 500-ml. two-necked round-bottomed flask is fitted with a reflux condenser to which is attached a calcium chloride drying tube. To the flask are added 124 g. (107 ml., 0.4 mole) of triphenyl phosphite and 85 g. (37 ml., 0.6 mole) of methyl iodide (Note 1), and a thermometer is inserted that is of sufficient length to extend into the liquid contents of the flask. The mixture is heated under gentle reflux by means of a heating mantle until the internal temperature has risen to about 120°, and the mixture is dark and viscous (Note 5). The flask is cooled, and 40 g. (0.4 mole) of cyclohexanol is added to the oily methyltriphenoxyphosphorus iodide. The mixture is shaken gently until homogeneous (Note 6) and allowed to stand overnight at room temperature (Note 7). The mixture is distilled through a 13-cm. Vigreux column (Note 8) to give 62.5–63 g. (74–75%) of iodocyclohexane, b.p. 66–68° (12 mm.),  $n_D^{22}$  1.5475.

## 2. Notes

1. The use of 1.2 instead of 1.5 equivalents of methyl iodide proved beneficial in some runs carried out by the checkers in which difficulty was experienced in reaching the recommended final temperature.

2. In order to obtain the yields cited, it is essential that the reaction temperature reaches the indicated final value, but heating should not be unnecessarily prolonged. The reaction is conveniently monitored by infrared spectroscopy. As the reaction proceeds, a broad, strong band at  $865\text{ cm.}^{-1}$  with a shoulder at  $880\text{ cm.}^{-1}$  disappears, and another broad, strong band at  $945\text{ cm.}^{-1}$  and a sharp, medium band at  $1310\text{ cm.}^{-1}$  appear.

3. Testing with ferric chloride is recommended.

4. The product contains about 5% of *t*-amyl iodide (n.m.r. spectrum); this is in agreement with the finding of Kornblum and Iffland,<sup>2</sup> who describe a simple way of removing this impurity.

5. As in procedure A the heat input should be increased from time to time, and it is essential to attain the recommended final temperature; unnecessarily prolonged heating after this is reached should be avoided as the phosphite methiodide decomposes at high temperatures.

6. With some alcohols (e.g., cyclohexanol) there is no appreciable rise in temperature, with others (e.g., *t*-amyl alcohol) it may be considerable, in which case the mixture should be cooled with water. In addition, there may be an induction period of up to 1 hour.

7. The reaction may be followed by infrared spectroscopy; a strong, broad band at  $1040\text{ cm.}^{-1}$  disappears, and a similar band appears at  $945\text{ cm.}^{-1}$ . The reaction appears to be complete after 6 hours.

8. It is not necessary to remove phenol from the reaction mixture containing alkyl iodides having a boiling point well below that of phenol. For isolation of the higher boiling alkyl iodides phenol should be removed by dissolving the reaction mixture in ether (400 ml.) and washing as in procedure A.

### 3. Discussion

The methods described above are applicable to almost any alcohol. Procedure A is best for sterically hindered alcohols and procedure B is especially useful for sensitive alcohols where rearrangement or alkene formation is likely. The submitter's

results for the conversion of a number of alcohols to the iodides on a preparative scale are summarized in Table I.

TABLE I  
IODIDES FROM ALCOHOLS

Iodide	Procedure	Yield, %	Boiling Point, °C.
<i>n</i> -Butyl iodide	A	80	126–128° (760 mm.)
<i>n</i> -Hexyl iodide	A	75	64–66° (15 mm.)
2-Phenylethyl iodide	A	95	94–95° (1.5 mm.)
1,3-Diiodo-2,2-dimethylpropane <sup>a</sup>	A	75	70–71° (0.1 mm.)
<i>t</i> -Amyl iodide	B	80	50–52° (50 mm.)
Ethyl 1-iodopropionate	B	90	65–66° (8 mm.)

<sup>a</sup> Reference 3.

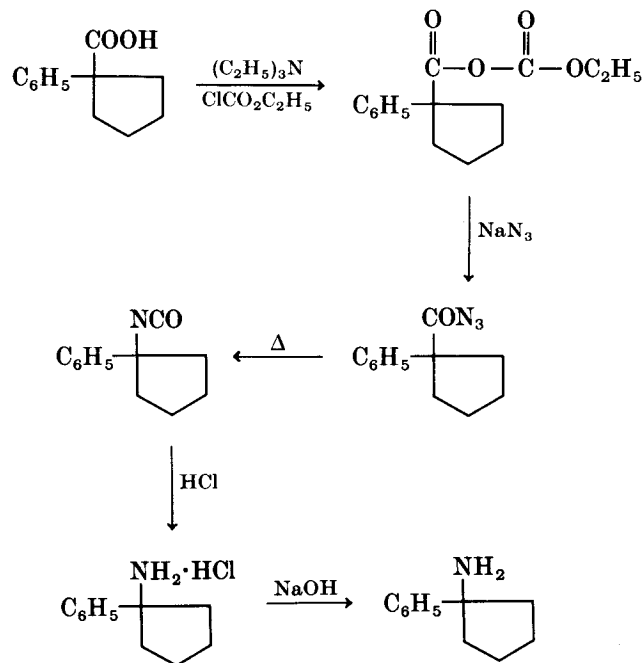
Landauer and Rydon<sup>4</sup> describe the application of the method, on a smaller scale, to numerous other iodides; they also prepared alkyl bromides and alkyl chlorides by substituting benzyl bromide and benzyl chloride, respectively, for methyl iodide.

The preparation of alkyl iodides by the phosphorus and iodine method is described in an earlier volume of *Organic Syntheses*.<sup>5</sup>

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AMINES FROM MIXED CARBOXYLIC-CARBONIC ANHYDRIDES:  
1-PHENYLCYCLOPENTYLAMINE



Submitted by CARL KAISER and JOSEPH WEINSTOCK<sup>1</sup>

Checked by A. BROSSI, R. A. MICHELI, and L. PORTLAND

### 1. Procedure

A 1-l. three-necked round-bottomed flask equipped with an air stirrer, dropping funnel, and low-temperature thermometer is charged with 38.0 g. (0.2 mole) (Note 1) of 1-phenylcyclopenten-

tanecarboxylic acid and 150 ml. of acetone. The mixture is stirred, and 22.3 g. (30.6 ml., 0.22 mole) of triethylamine is added over 5 minutes (a  $2^\circ$  rise in temperature is observed). The solution is chilled to  $-5$  to  $0^\circ$  in an ice-salt bath, and 24.0 g. (21.1 ml., 0.22 mole) of ethyl chlorocarbonate (Note 2) in 50 ml. of acetone is added slowly (25 minutes) so as to maintain the temperature between  $-5$  to  $0^\circ$ . After the addition is complete, the cold mixture is stirred for an additional 15 minutes. A solution of 26.0 g. (0.4 mole) of sodium azide in 75 ml. of water is then added over a 25-minute period while the temperature is kept at  $-5$  to  $0^\circ$ . The mixture is stirred for 30 minutes longer at this temperature, poured into 750 ml. of ice water, and shaken with four 250-ml. portions of toluene (Note 3). The combined toluene extracts are dried over anhydrous magnesium sulfate and transferred to a 2-l. three-necked round-bottomed flask equipped with a two-necked Claisen-type adapter, stirrer, and reflux condenser. The stirred solution is heated cautiously (Note 4) under reflux for 1 hour on a steam bath (nitrogen evolution is observed initially). The toluene is then removed by distillation at  $50^\circ$  by use of a rotary evaporator attached to a water aspirator. The flask containing the residual oily isocyanate is again fitted with the Claisen-type adapter, stirrer, and reflux condenser. The oil is stirred, cooled in an ice bath, and 300 ml. of 8*N* hydrochloric acid solution (Note 5) is added. The cooling bath is removed, the stirred mixture is gradually heated on a steam bath (Note 6) until carbon dioxide evolution has subsided (30 minutes), and the solution is then heated under reflux for 10 minutes. The flask is evacuated by means of a water aspirator and warmed in a bath at  $50^\circ$  for about 10 minutes. About 10–20 ml. of distillate is collected, and a crystalline product separates (Note 7). Ice water (200 ml.) is added to the flask with cooling in an ice bath, and 1 l. of 2.5*N* sodium hydroxide solution is added slowly to pH 12. The mixture is shaken with three 200-ml. portions of ether, the combined extracts are dried over anhydrous magnesium sulfate, and the ether is removed by distillation at  $50^\circ$  by use of a water aspirator to yield 29.7 g. of an oil. Distillation of the crude product

gives 24.5–26.1 g. (76–81%) of 1-phenylcyclopentylamine, b.p. 112–114° (9 mm.),  $n_{D}^{20}$  1.5439 (Note 8).

## 2. Notes

1. 1-Phenylcyclopentanecarboxylic acid,<sup>2,3</sup> m.p. 157–159°, was obtained from Aldrich Chemical Company, Inc.

2. A commercial grade of ethyl chlorocarbonate, stabilized with calcium carbonate, was employed without purification.

3. Approximately 3.6–3.9 g. of 1-phenylcyclopentanecarboxylic acid (m.p. 158–159.5°) can be recovered by acidification of the aqueous solution which remains after washing with toluene.

4. Rearrangement of the azide must be carried out carefully as the reaction is exothermic, and a large volume of nitrogen is evolved. The submitters have encountered no difficulties if the described dilution, that is, 0.2 mole of azide in 1 l. of toluene, is employed. The steam bath should be replaced by a cooling bath if the solution refluxes vigorously.

5. Approximately 8*N* hydrochloric acid solution was prepared by addition of 100 ml. of water to 200 ml. of 37.5% hydrochloric acid.

6. Heating should be gradual and in a large reaction vessel as hydrolysis of isocyanate is accompanied by evolution of carbon dioxide and considerable foaming may occur. If excessive foaming occurs, the steam bath should be removed.

7. The checkers carried the synthesis through to this point without interruption. Since this required about 8 hours on the scale described, the equipment and chemicals were made ready the preceding day.

8. Nuclear magnetic resonance spectrum (deuteriochloroform-solvent, internal tetramethylsilane reference): multiplet at 7.33 p.p.m. (5H, aromatic protons), broad singlet at 1.83 p.p.m. (8H, cyclopentane protons) and singlet at 1.30 p.p.m. (2H, amino protons). The distilled product was of high purity by gas chromatography analysis. A 122 cm. × 6.4 mm. o.d. stainless steel column containing 3% SE-30 on Diatoport S (80–100 mesh) and programmed from 100–200° at 10°/minute was used. The retention time is about 5 minutes.

## 3. Discussion

1-Phenylcyclopentylamine has also been prepared from 1-phenylcyclopentanecarboxylic acid by means of the Hofmann degradation of the intermediate amide<sup>4,5</sup> and from the intermediate carboxylic acid chloride by the Curtius reaction.<sup>6</sup> In the method described, using the mixed carboxylic-carbonic anhydride,<sup>7</sup> improved yields of the amine are obtained.

The usual procedure of preparing acid azides, which involves treating an acid chloride with sodium azide,<sup>8,9</sup> suffers from the disadvantage that it is often difficult to obtain pure acid chlorides in good yields from acids which either decompose or undergo isomerization in the presence of mineral acids.<sup>7</sup> Synthesis of the azide by way of the ester and hydrazide<sup>10</sup> has been used to circumvent this difficulty but is much less convenient. The present procedure permits ready formation of acid azides in excellent yields from mixed carboxylic-carbonic anhydrides and sodium azide under very mild conditions.

A possible limitation to this procedure, however, is that it is dependent upon the relative reactivity of the two carbonyl groups of the mixed carboxylic-carbonic anhydride toward the azide anion. Although either carbonyl group may be attacked by the azide ion, an attack on the more electrophilic carbonyl group is usually strongly favored and high yields of the acid azides generally result. Steric considerations may be important however. Preference for azide attack on even a somewhat hindered carboxylic carbonyl is illustrated by the present example in which this group is proximal to phenyl and cyclopentyl groups.

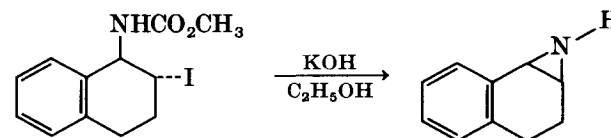
This modification of the Curtius reaction has been used extensively in many laboratories and has been found to be generally applicable. Some examples from the literature include the stereoselective synthesis of a wide variety of cyclopropylamine derivatives from the corresponding acids,<sup>11–13</sup> the stereoselective preparation of some substituted norbornylamines from easily isomerized acids,<sup>14</sup> the preparation of some 1-aminocyclobutanecarboxylic acids from the corresponding acid esters,<sup>15</sup> the preparation of a substituted cyclobutanone from

the corresponding cyclobutane-1,1-dicarboxylic acid via the 1,1-diamine,<sup>16</sup> and the preparation of a variety of heterocyclic amines from the corresponding acids.<sup>17-19</sup>

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## AZIRIDINES FROM $\beta$ -IODOCARBAMATES:

### 1,2,3,4-TETRAHYDRONAPHTHALENE(1,2)IMINE



Submitted by C. H. HEATHCOCK<sup>1</sup> and A. HASSNER<sup>2</sup>

Checked by WILLIAM G. KENYON and RICHARD E. BENSON

### 1. Procedure

To a solution of 25 g. of potassium hydroxide in 250 ml. of 95% ethanol in a 500-ml. round-bottomed flask equipped with a reflux condenser is added 16.6 g. (0.05 mole) of methyl (*trans*-2-iodo-1-tetralin)carbamate (Note 1). The resulting mixture is heated under reflux on a steam bath for 2 hours, cooled, and added to 500 ml. of water. The clear yellow solution is shaken three times with 100-ml. portions of ether. The ether layers are combined and washed three times with 125-ml. portions of water and a single time with 125 ml. of a saturated sodium chloride solution. The ether layer is dried over 5 g. of anhydrous potassium carbonate. The drying agent is removed by filtration, and the ether is removed by distillation on a steam bath to give the crude imine as a yellow-brown oil (Note 2). The oil is transferred to a small flask, the container is rinsed with ether, and the rinse is added to the distillation flask. The product is collected by distillation through a small Vigreux column with warm water circulating through the condenser to prevent crystallization of the product. The fraction boiling at 80–82° (0.15–0.25 mm.) is collected as a solid that forms in the receiver, m.p. 54–56°. The yield of imine is 4.9–5.1 g. (68–70%) (Note 2). The infrared spectrum has a band at 3205 cm.<sup>-1</sup> (NH) (Note 3).

## 2. Notes

1. C. H. Heathcock and A. Hassner, *Org. Syn.*, this volume, p. 112.

2. The submitters state that product of m.p. 49–51° can be obtained by direct crystallization of the oil. The oil from a run conducted on a scale twice that described above is cooled to –15° and 30 ml. of pentane is added. Upon scratching the flask, the product crystallizes and is collected by filtration and washed with a little cold pentane. The yield is 9–10 g. (62–69%), m.p. 49–51°.

3. The n.m.r. spectrum (carbon tetrachloride solution, tetramethylsilane reference) shows a broad singlet centered at 0.7 p.p.m. (1H) and complex multiplets at 1.1–3.05 (6H) and 6.76–7.30 p.p.m. (4H).

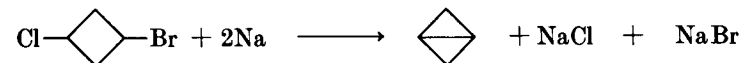
## 3. Discussion

The procedure reported here, which is that of Hassner and Heathcock,<sup>3</sup> is more convenient than the Wenker synthesis of aziridines<sup>4</sup> and appears to be more general.<sup>5</sup> It represents a simple route from olefins to aziridines (via  $\beta$ -iodo carbamates).<sup>3,5,6</sup> Aziridines are also useful as intermediates in the synthesis of amino alcohols and heterocyclic systems.<sup>5,7–9</sup>

1. Department of Chemistry, University of California, Berkeley, California 94720.
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## BICYCLO[1.1.0]BUTANE

(Bicyclo[1.1.0]butane)



Submitted by GARY M. LAMPMAN and JAMES C. AUMILLER<sup>1</sup>

Checked by R. A. FENOGLIO and K. B. WIBERG

## 1. Procedure

A 300-ml. three-necked round-bottomed flask is equipped with a mechanical stirrer, a reflux condenser, and a pressure-equalizing addition funnel. The condenser is connected in series with two traps, immersed in liquid nitrogen, with the exit leading to a drying tube (Note 1). A line for dry nitrogen that has a T-tube joined to a U-tube containing mercury is connected to the top of the addition funnel (Note 2). To the flask are added 150 ml. of purified dioxane (Note 3) and 13.6 g. (0.59 g. atom) of freshly cut sodium (Note 4). The mixture is heated to reflux, and the molten sodium is broken up with the stirrer. To the refluxing dioxane is added 20.0 g. (0.118 mole) of 1-bromo-3-chlorocyclobutane (Note 5) in 20 ml. of dioxane (Note 3) over a 1-hour period and refluxing is maintained for another 2 hours (Notes 6 and 7). The product in the traps is separated from any dioxane by means of the vacuum manifold system shown in Figure 1 (Note 8). The two traps containing the product are cooled in liquid nitrogen and connected to one of the stopcocks on the manifold. A gas storage bulb (Figure 2) is attached to the other stopcock. All the stopcocks are opened, and the system is evacuated. The stopcock to the pump is then closed, and the liquid nitrogen bath is removed from the traps and is used to cool the gas storage bulb. The traps are warmed slightly, and the bicyclobutane condenses in the storage bulb, leaving the dioxane behind. The yield of bicyclobutane is 5–6 g. (78–94%) (Note 9).

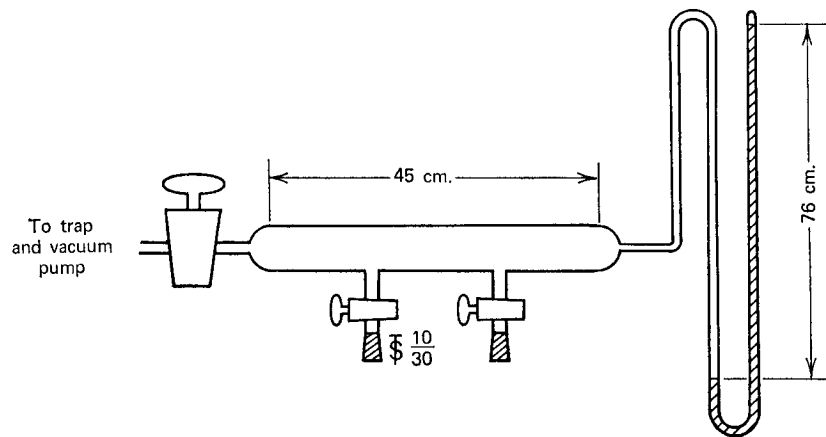


Figure 1. Vacuum manifold.

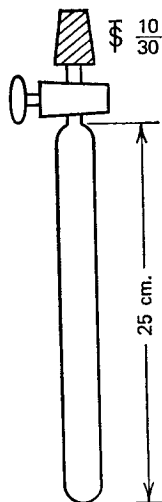


Figure 2. Gas storage bulb.

## 2. Notes

1. Although the entire gaseous product is caught in the first trap, this trap tends to plug during the reaction. Therefore, the second trap is used as a safety measure to collect the bicyclobutane as the first trap is thawed to open the system.

2. It is essential that a U-tube containing mercury is connected by a T-connector to the nitrogen inlet. The U-tube serves to monitor the pressure on the system and acts as a safety valve in the event of a plugged trap. A slight positive pressure is maintained.

3. Reagent-grade dioxane (2 l.) is heated to reflux with the sodium ketyl of benzophenone prepared from 10 g. of benzophenone and 1 g. of sodium until a deep blue solution results. If the color is not developed, another portion of benzophenone and sodium is added and the heating continued until the color persists. The peroxide-free dioxane is distilled from the flask and is used immediately.

4. The excess sodium allows the reaction to proceed at a greater rate and decomposes any remaining peroxides in the dioxane.

5. G. M. Lampman and J. C. Aumiller, *Org. Syn.*, this volume, p. 106.

6. The reflux rate and flow of nitrogen gas must be kept at a minimum to assure that the amount of dioxane carried over to the traps in liquid nitrogen is kept as small as possible.

7. This reflux time is a minimum since decreased yields were observed when the reflux time was shortened. There is no increase in yield when the refluxing time is increased to 4 hours.

8. The basic apparatus consists of a large diameter (about 25 mm.) glass tube to which are attached at least two stopcocks, a closed-end manometer, and a large stopcock, which is used to isolate the manifold from the vacuum pump.

9. The product, which is about 90% bicyclobutane and 10% cyclobutene, is sufficiently pure for most purposes. The purity of the product can be determined by gas chromatography analysis at room temperature, using a 275-cm.-long column containing 20%  $\beta,\beta'$ -oxydipropionitrile on Chromosorb W (45/60). The retention times are 2.7 and 3.8 minutes for cyclobutene and bicyclobutane, respectively. Bicyclobutane (b.p.  $8^\circ$ ) can be stored temporarily in the gas storage bulb as a liquid in a dry ice-acetone bath or for longer periods of time in an ampoule, sealed under vacuum, and stored in a freezer.

### 3. Discussion

Bicyclobutane has been prepared by intramolecular addition of a divalent carbon to an olefinic double bond,<sup>2</sup> irradiation of butadiene,<sup>3</sup> decomposition of cyclopropanecarboxaldehyde tosylhydrazone,<sup>4</sup> and deamination of cyclobutylamine and cyclopropylcarbinylamine.<sup>5</sup> The present procedure is based upon a published method.<sup>6</sup> This procedure gives the highest yield of the known methods and provides a process for making moderate quantities of material.

The procedure provides a good example of a high-yield intramolecular Wurtz reaction. Intermolecular Wurtz reactions normally do not give high yields of coupled products and are accompanied by formation of alkenes and alkanes corresponding to the alkyl halide.<sup>7</sup> In contrast, intramolecular reactions of 1,3-dihalides with metals such as sodium are important synthetic methods for making cyclopropane derivatives. Examples are the reactions of sodium with pentaerythrityl tetrabromide to give spiropentane<sup>8</sup> and of sodium-potassium alloy with 1,3-dibromohexamethylcyclobutane to give hexamethylbicyclo[1.1.0]-butane.<sup>9</sup> If 1,3-dihalides are not used, the yields of cyclic compounds may be considerably reduced. Thus 1,4-dibromobutane<sup>10</sup> and 3-(bromomethyl)cyclobutyl bromide<sup>11</sup> give very little cyclobutane and bicyclo[1.1.1]pentane, respectively.

Metals other than sodium may be considered for the reduction in intramolecular Wurtz reactions.<sup>11</sup> One of the most common of these is zinc under various reaction conditions. Examples of use of this reagent that have resulted in high yields of cyclopropane and derivatives of cyclopropane include cyclopropane from 1,3-dichloropropane,<sup>12</sup> spiropentane from pentaerythrityl tetrabromide in the presence of a chelating agent,<sup>13</sup> spiro[2.5]octane from 1,1-bis-(bromomethyl)cyclohexane,<sup>14</sup> and 1,1-dialkylcyclopropanes from 1,3-dibromo-2,2-dialkylpropanes.<sup>14</sup> However, 1-bromo-3-chlorocyclobutane yields no bicyclobutane on reaction with zinc,<sup>6</sup> even in the presence of a chelating agent.

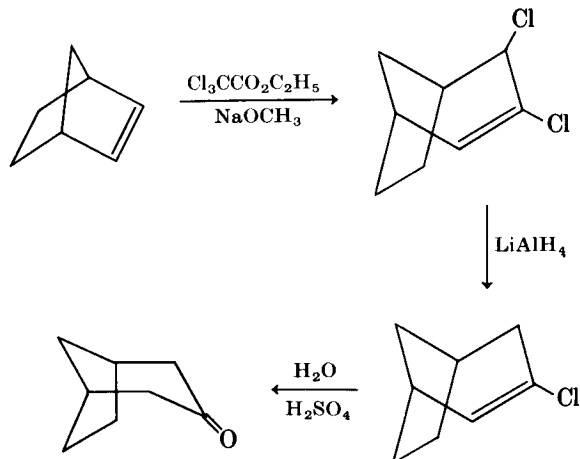
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2. D. M. Lemal, F. Menger, and G. W. Clark, *J. Amer. Chem. Soc.*, **85**, 2529 (1963).

## BICYCLO[3.2.1]OCTAN-3-ONE

(Bicyclo[3.2.1]octan-3-one)



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 Checked by R. W. BEGLAND and R. E. BENSON

## 1. Procedure

A. *exo*-3,4-Dichlorobicyclo[3.2.1]oct-2-ene. A 1-l. four-necked round bottomed flask is fitted with an efficient stirrer, a thermometer, a reflux condenser protected by a calcium chloride tube, and a 500-ml. stoppered addition funnel equipped with a pressure-equalizing side tube. After the addition of a solution of 52.5 g. (0.56 mole) of norbornene (Note 1) in 400 ml. of petroleum ether (Note 2, b.p. 45–60°) to the flask, 112 g. (2.06 moles) of sodium methoxide (Note 3) is added, and stirring is begun. The flask is immersed in an ice-salt mixture (Note 4). Three hundred forty-nine grams (1.8 moles) of ethyl trichloroacetate (Note 5) is placed in the addition funnel and allowed to drip slowly into the stirred mixture at a rate such that the temperature does not rise above 0° (Note 6). The addition requires about 4 hours, and the originally white reaction mixture becomes increasingly yellow in color. The mixture is stirred at a temperature below

0° for 4 hours (Note 6), and then the temperature is allowed to rise gradually to room temperature overnight. The reaction mixture is poured onto a mixture of 500 g. of crushed ice and 300 ml. of water. After the ice has melted, the organic layer is separated, and the aqueous layer is shaken with four 200-ml. portions of ether. The aqueous layer is neutralized with 10% hydrochloric acid and is shaken again with two 200-ml. portions of ether. The original organic layer and the ether extractions are combined, washed with 300 ml. of a saturated solution of sodium chloride, and dried for 6 hours over 20 g. of anhydrous magnesium sulfate. The drying agent is removed by filtration, and the solution is concentrated to about 200 ml. by distillation. The resulting product is distilled through a 20-cm. Vigreux column to give 72.5–87.0 g. (74–88%) of *exo*-3,4-dichlorobicyclo[3.2.1]oct-2-ene as a colorless liquid, b.p. 72–73° (0.9 mm.),  $n_D^{25}$  1.5333 (Notes 7 and 8).

B. 3-Chlorobicyclo[3.2.1]oct-2-ene. To a 2-l. three-necked round-bottomed flask equipped with a stirrer, a reflux condenser protected by a calcium chloride tube, and a 500-ml. stoppered addition funnel equipped with a pressure-equalizing tube is added 350 ml. of dry ether and 15 g. (0.396 mole) of powdered lithium aluminum hydride (Note 9). The flask is placed in a mixture of ice and water, and 1050 ml. of dry tetrahydrofuran (Note 10) is added. Stirring is begun, and a solution of 39.5 g. (0.224 mole) of *exo*-3,4-dichlorobicyclo[3.2.1]oct-2-ene in 50 ml. of dry tetrahydrofuran (Note 10) is added dropwise from the addition funnel over a 30-minute period. After the addition is complete, the reaction mixture is heated under gentle reflux for 18 hours. The mixture is then cooled to 0°, and the remaining lithium aluminum hydride is decomposed by the careful addition of wet ether followed by the cautious dropwise addition of 10 ml. of water. The resulting mixture is poured onto a mixture of 500 g. of crushed ice and 200 ml. of water. After the ice has melted, the organic layer is separated, and the aqueous layer is acidified to a pH of 5–6 with 10% hydrochloric acid solution to dissolve the lithium and aluminum salts present (Note 11). The aqueous solution is shaken five times with 200-ml. portions of ether. The organic layers are combined and washed

with 200 ml. of a saturated solution of sodium chloride and dried overnight over 20 g. of anhydrous magnesium sulfate. The ether and tetrahydrofuran are removed by distillation at atmospheric pressure, and the product is distilled through a 20-cm. Vigreux column to give 23.5–23.9 g. (74–75%) of 3-chlorobicyclo[3.2.1]oct-2-ene as a colorless oil, b.p. 76–77° (21 mm.),  $n_D^{20}$  1.5072 (Note 12).

C. *Bicyclo[3.2.1]octan-3-one*. A magnetic stirring bar is placed in a 300-ml. round-bottomed flask and 100 ml. of concentrated sulfuric acid (Note 13) is added. Stirring is begun, the flask is cooled in an ice bath, and 9.0 g. (0.63 mole) of 3-chlorobicyclo[3.2.1]oct-2-ene is added in one portion. The mixture is stirred and allowed to warm slowly over 4 hours to room temperature and then stirred overnight. The resulting solution is poured onto 200 g. of ice with stirring. After the ice has melted, the mixture is shaken with three 100-ml. portions of ether. The ether layers are combined, washed once with 50 ml. of water, and dried over 10 g. of magnesium sulfate. The ether is removed by careful distillation, and the crude product is sublimed at a bath temperature of 70° (15 mm.) directly onto a cold finger inserted into the flask. The crude product is twice sublimed to give 5.9–6.3 g. (75–81%) of bicyclo[3.2.1]octan-3-one, m.p. 137°, of 98% purity as judged by gas chromatography analysis (Notes 14, 15, and 16).

## 2. Notes

1. Norbornene can be prepared by the Diels-Alder reaction of ethylene with dicyclopentadiene.<sup>4</sup> It can be purchased from Matheson Coleman and Bell or the Aldrich Chemical Company, Inc.

2. The petroleum ether used must be olefin-free.

3. The submitters used sodium methoxide available from Schuchardt, Ainmillerstrasse 25, 8-Munich 13, Germany. The checkers used product available from Matheson Coleman and Bell.

4. An amount sufficient to fill a 5-l. container is recommended.

5. It is used as purchased from either Schuchardt or Eastman

Organic Chemicals. It appears that when equimolar amounts of carbene precursor and olefin are used, the adduct is obtained in only 25% yield.<sup>5</sup>

6. Efficient stirring and maintenance of a low temperature are required if high yields are to be obtained.

7. For the final distillation the pressure is regulated by means of a manostat.

8. The infrared spectrum (neat) shows absorption at 1645, 1450, 1305, 1223, 1052, 974, 959, 866, 796, and 750  $\text{cm}^{-1}$ . The n.m.r. spectrum (carbon tetrachloride solution, tetramethylsilane reference) shows absorption at 6.08 (doublet,  $J \sim 7.0$  Hz.) and 4.1 p.p.m. (doublet,  $J \sim 3$  Hz.) attributable to the vinyl and allyl protons, respectively.

9. This was purchased from Metal Hydrides, Inc., and is also obtainable from Schuchardt.

10. The checkers used reagent-grade tetrahydrofuran (available from Fisher Scientific Company) from a freshly opened bottle. The submitters used tetrahydrofuran purified as described in L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed., Revised, D. C. Heath and Co., Boston, 1957, p. 292. (See *Org. Syn.*, **46**, 105 (1966) for a warning regarding the purification of tetrahydrofuran.)

11. A small amount of insoluble material may remain at this point. If it interferes with the extraction procedure it may be removed by filtration.

12. The infrared spectrum (neat) shows absorption at 1635, 1440, 1038, 952, 841, 833, and 685  $\text{cm}^{-1}$ . The n.m.r. spectrum (carbon tetrachloride solution, tetramethylsilane reference) has a doublet at 5.91 p.p.m. ( $J \sim 7.0$  Hz.) due to the vinyl proton and three major peaks in the 2.0–2.8 p.p.m. region.

13. Sulfuric acid of specific gravity 1.84 is used.

14. The infrared spectrum, determined in nujol, has an intense band at 1710  $\text{cm}^{-1}$ . The n.m.r. spectrum (deuteriochloroform solution, tetramethylsilane reference) has a broad peak at 1.7 p.p.m. (6H), a sharp peak at 2.35 p.p.m. (4H) and a broad peak at 2.55 p.p.m. (2H).

15. The gas-chromatography data were obtained using 3 m.  $\times$  7 mm. column packed with nonacid-washed Chromosorb



45/60 W containing 15% 200M Apiezon silicone oil as the immobile phase.

16. The oxime has m.p. 96°. The ketone can be further purified by means of the semicarbazone derivative, which can be purified by crystallization and subsequently hydrolyzed by dilute hydrochloric acid.

### 3. Discussion

Studies by the submitters have indicated that the procedure reported here is the preferred method for the preparation of bicyclo[3.2.1]octan-3-one. It employs readily available, inexpensive reagents, and the overall yield is good. In addition, the method can be used for the synthesis of the difficultly accessible next higher homologues of bicyclo[2.2.2]oct-2-ene as well as for derivatives of norbornene. Bicyclo[3.2.2]nonan-3-one and 1-methylbicyclo[3.2.1]octan-3-one have been prepared by a similar route<sup>6</sup> in 60% and 47% yields, respectively (based on adduct). However, the preferred procedure for the formation of the dichlorocarbene adduct of bicyclo[2.2.2]oct-2-ene is that of Seyferth using phenyltrichloromethylmercury. Even in this case the overall yield is moderate (37%).

The present procedure is a refinement of existing methods.<sup>6-9</sup> It is an adaption of the method of Parham and Schweizer<sup>10</sup> and furnishes the carbene adduct in higher yield than other methods. The submitters' studies indicate that the procedure of Doering,<sup>11</sup> involving the interaction of chloroform with potassium *t*-butoxide, is unsatisfactory since traces of *t*-butanol present react with the rearranged adduct during the reduction step. In addition, the yields of adduct are poor (4-15%).<sup>5</sup> The method of Wagner,<sup>12</sup> utilizing the pyrolysis of sodium trichloroacetate, is easy to perform, but the yields of initial adduct are poor (13%). That of Seyferth<sup>13</sup> involving the pyrolysis of phenyltrichloromethylmercury gives the adduct in 45% yield. However, the higher cost and additional steps entailed in the preparation of the reagent, together with the hazards associated with employing mercury, detract from its use.

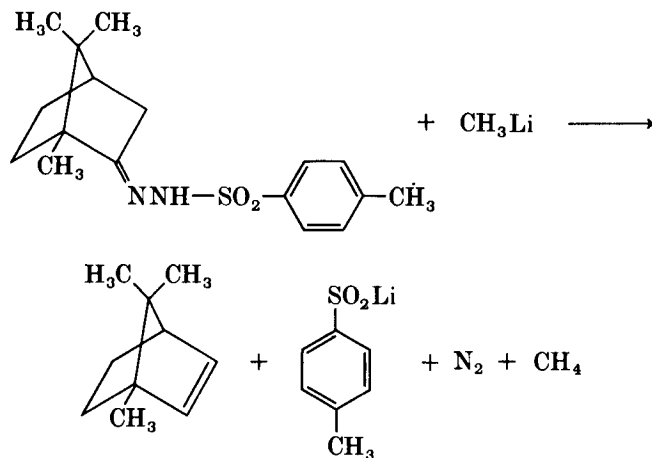
Other preparations leading to bicyclo[3.2.1]octan-3-one include the oxidation of the mixture of alcohols obtained by the action

of nitrous acid on 2-aminomethylnorbornane,<sup>14</sup> the chromic acid oxidation of bicyclo[3.2.1]octane,<sup>15</sup> and the oxidative hydroboration of bicyclo[3.2.1]oct-2-ene.<sup>16</sup> These reactions lack preparative utility and all have a common disadvantage of being accompanied by isomer formation.

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## 2-BORNENE

(Bornylene; 1,7,7-Trimethylbicyclo[2.2.1]hept-2-ene)

Submitted by ROBERT H. SHAPIRO and J. H. DUNCAN<sup>1</sup>

Checked by ROBERT CZARNY and ROBERT E. IRELAND

## 1. Procedure

In a dry 1-l. three-necked flask, fitted with a reflux condenser protected with a calcium sulfate-containing drying tube, a 250-ml. pressure-equalizing dropping funnel, and containing a magnetic stirring bar, are placed 32 g. (0.1 mole) of camphor tosylhydrazone (Note 1) and 400 ml. of dry ether (Note 2). The flask is immersed in a cold-water bath (20–25°), and the contents stirred magnetically. About 50 ml. of dry ether is placed in the dropping funnel, and the addition rate is set at 2–3 ml./minute (Note 3). After this addition 150 ml. of 1.6*N* (0.24 mole) methyllithium (Note 4) in ether is added to the dropping funnel and allowed to drop into the reaction flask during 1 hour (Note 5), while the cooling bath temperature is maintained at 20–25°. The yellow-orange solution is stirred for 8–9 hours, during which time lithium *p*-toluenesulfinate precipitates, and the solution develops a deep red-orange color. A

small amount of water is carefully added to destroy the excess methyllithium, and then an additional 200 ml. is added. The layers are separated, the organic phase is washed four times with 250-ml. portions of water, and the combined aqueous phases are shaken twice with 100-ml. portions of ether. After drying the combined ethereal extracts over anhydrous sodium sulfate, the volume of the solution is reduced to 50–60 ml. by distillation of the ether through a 25-cm. Vigreux column with gentle boiling on a steam bath. To the resulting orange solution is added 100 ml. of distilled pentane (Note 6), and the solvent is again gently boiled away to reduce the volume to 30–50 ml. The addition and removal of pentane are repeated two additional times to assure the complete removal of ether, and then the final volume of the solution of 2-bornene is reduced to about 30–40 ml. The solution is added to an 80 × 5 cm. chromatography column containing 500 g. of alumina (Note 7), and the product is eluted with 750 ml. of pentane. After concentration of the eluate by distillation of the solvent through a Vigreux column, the residue is transferred to a 50-ml. flask and distilled through a U-tube with the aid of an oil bath and a heating lamp (Note 8). After collecting a fore-run (pentane and 2-bornene), 2-bornene is collected in a cooled flask (Note 9) as colorless crystals. The yield of 2-bornene is 8.5–8.8 g. (63–65%), m.p. 110–111° (reported<sup>2</sup>: 109–110°). Gas chromatographic analysis<sup>3</sup> shows this product is 98–99% pure and contains no camphene or tricyclene (Note 10).

## 2. Notes

1. Camphor tosylhydrazone<sup>4</sup> is prepared in the following manner. To a 1-l. one-necked round-bottomed flask are added 44 g. (0.24 mole) of *p*-toluenesulfonylhydrazide,<sup>5</sup> 31.6 g. (0.20 mole) of camphor, and 300 ml. of 95% ethanol. One milliliter of concentrated hydrochloric acid is added, and the flask is fitted with a reflux condenser. The solution is heated under reflux for 2 hours. The resulting solution is cooled in an ice bath, and the colorless needles are collected by suction filtration and dried in air (Note 11). Recrystallization from ethanol yields 50 g. (73%) of pure camphor tosylhydrazone, m.p. 163–164°.

2. Anhydrous ether available from Mallinckrodt Chemical Works can be used without further drying.

3. This prevents clogging of the funnel during the subsequent addition of methylolithium solution.

4. Methylolithium available from either Foote Mineral Company or Alfa Inorganics, Inc. can be used without further purification. The checkers used 137 ml. of a 1.85*M* solution.

5. During the first half of the addition each drop of methylolithium solution produces a yellow color that quickly disappears. The solution turns yellow during the second half of the addition and slowly becomes more intensely colored until it reaches red-orange near the end of the reaction period.

6. Since the solvent is never completely removed at any time prior to final distillation of the product, the accumulation of higher boiling hydrocarbons results if petroleum ether is used. As a result the fore-run of the final distillation will be larger, and the yield of 2-bornene will be reduced. The pentane was distilled to assure the removal of any higher boiling impurities.

7. Neutral, reagent-grade aluminum oxide available from Merck & Co., Inc. was used by the checkers.

8. When the temperature of the bath reaches 140–143°, the heating lamp is turned directly on the U-tube, and the receiver is changed to collect the 2-bornene.

9. The yield of the product is greatly reduced if the receiver is not cooled. A dry ice-isopropyl alcohol bath was used.

10. On a 180 cm. × 32 mm. gas chromatography column containing 10% Apiezon L on Chromosorb P at 60° a synthetic mixture of 2-bornene (10.3 minutes), tricyclene (12.3 minutes), and camphene (15.5 minutes) was readily resolvable.

11. The product has m.p. 161–163° and can be used without further purification.

### 3. Discussion

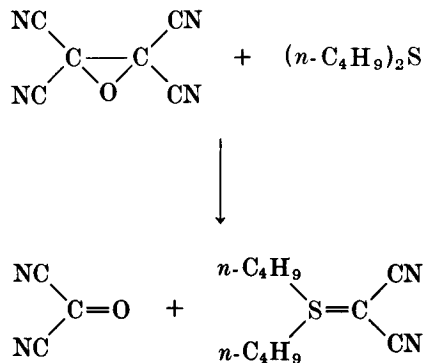
2-Bornene has been prepared from the reaction of 2-bromobornane-3-carboxylic acid with aqueous sodium bicarbonate,<sup>6</sup> by pyrolysis of isoborneol methyl xanthate,<sup>7</sup> and by the  $\beta$ -elimination of hydrogen chloride from bornyl chloride with sodium alkoxides in various solvents.<sup>2</sup>

This procedure appears to be general for the preparation, without rearrangement, of lesser substituted olefins. 2-Methylcyclohexanone tosylhydrazone gives 3-methylcyclohexene (98% yield by gas chromatography analysis).<sup>8</sup> Cholestan-6-one tosylhydrazone gives  $\Delta^6$ -cholestene (95% isolated yield), androstan-17-one tosylhydrazone gives  $\Delta^{16}$ -androstene (91% isolated yield),<sup>8</sup> and phenylacetone tosylhydrazone gives allylbenzene (70% yield by gas chromatography analysis, accompanied by the substitution product isobutylbenzene in 30% yield). Another advantage of this procedure is its simplicity and the use of readily available carbonyl compounds as precursors. The reaction proceeds smoothly but more slowly at –25° and can be employed with heat-sensitive or volatile compounds in ordinary laboratory equipment.

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2. (a) H. Meerwein and J. Joussen, *Ber.*, **55**, 2529 (1922); (b) M. Hanack and R. Hähnle, *Chem. Ber.*, **95**, 191 (1962); (c) L. Borowiecki and Y. Chrétien-Bessière, *Bull. Soc. Chim. Fr.*, 2364 (1967).
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## CARBONYL CYANIDE

(Mesoxalonitrile)

Submitted by E. L. MARTIN<sup>1</sup>

Checked by R. KOTTKE and W. D. EMMONS

## 1. Procedure

*Caution! Carbonyl cyanide and water react with explosive violence to form hydrogen cyanide and carbon dioxide. This preparation should be carried out in a good hood with shielding, and rubber gloves should be worn.*

A 500-ml. three-necked flask equipped with a magnetic stirring bar, a pressure-equalizing dropping funnel, a thermometer, and a 25-cm. Vigreux column attached to a trap cooled in a dry ice-acetone mixture is charged with 100 ml. of diethyl phthalate (Note 1) and 43 g. (0.3 mole) of tetracyanoethylene oxide (Note 2). The dropping funnel is charged with 44 g. (0.3 mole) of distilled *n*-butyl sulfide, the pressure is reduced to 5–20 mm. by means of a water aspirator, and the reaction flask is warmed with a water bath at 50°. The *n*-butyl sulfide is added dropwise with stirring over 20–25 minutes, and the internal temperature is maintained at  $50 \pm 2^\circ$  by controlling the temperature of the water bath. The reaction is exothermic at the start, but it is necessary to supply heat toward the end of

the addition. The internal temperature is increased to 80° over 10–15 minutes after the sulfide has been added. The vacuum on the system is released by the introduction of nitrogen. The solid carbonyl cyanide that has collected in the trap is allowed to warm to room temperature under nitrogen, and 2 g. of tetracyanoethylene oxide (Note 3) and a boiling stone are added. The mixture is then warmed to 50°, and the product is distilled under reduced pressure (5–20 mm.) into a second trap cooled in a dry ice-acetone mixture. Another portion of tetracyanoethylene oxide (1 g.) is added to the distillate, and the carbonyl cyanide is distilled again under reduced pressure (5–20 mm.) into a distillation flask cooled in a dry ice-acetone mixture. Fractionation of the distillate through a 20-cm. column packed with glass helices gives 20.8–21.8 g. (86–91%) (Note 4) of faintly yellow carbonyl cyanide, b.p. 65–66° (Notes 5, 6, and 7).

## 2. Notes

1. The diethyl phthalate is freed of traces of water and ethanol by distilling about 5% of it under reduced pressure, b.p. 185° (20 mm.) and then cooling the residue with protection from moisture. Moisture must be excluded because carbonyl cyanide reacts vigorously with water.

2. W. J. Linn, *Org. Syn.*, **49**, 103 (1969).

3. The distillate is treated with tetracyanoethylene oxide to remove the small amount of *n*-butyl sulfide that codistills with carbonyl cyanide.

4. The yield is based on the amount of tetracyanoethylene oxide initially charged.

5. There is very little if any low-boiling material when the reaction is carried out as described and care is taken to have the apparatus dry and to exclude moisture.

6. Gas chromatographic analyses of various cuts indicate essentially pure carbonyl cyanide with traces of hydrogen cyanide and carbon dioxide. Both are hydrolysis products of carbonyl cyanide and probably are formed because of traces of moisture on the column.

7. Carbonyl cyanide has m.p.  $-38^\circ$ ,  $n_D^{20}$  1.3923.<sup>2</sup>

### 3. Discussion

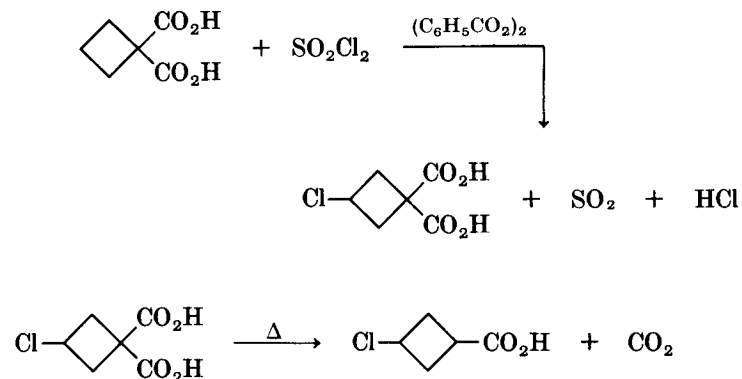
The procedure described is that of Linn, Webster, and Benson.<sup>3</sup> Carbonyl cyanide has previously been prepared by the pyrolysis of the diacetyl derivative of diisonitrosoacetone, a multistep process that suffers from low yield, lack of reproducibility, and risk of explosion.<sup>2</sup> The present procedure provides a convenient high-yield synthesis of carbonyl cyanide.

Carbonyl cyanide reacts with alcohols and phenols to give cyanofomate esters,<sup>4</sup> with primary and secondary amines to give cyanofomamides, with N,N-dimethylaniline to give bis[*p*-(dimethylamino)phenyl]malononitrile and with pyrrole to give 2-(cyanoformyl)pyrrole.<sup>5</sup> With olefins of the type C=C—CH<sub>2</sub>, products of structures C=CC—C(CN)<sub>2</sub>OH, C=CC—COCN, and C=CC—C(CN)<sub>2</sub>OCOCN are obtained, depending on the nature of the olefin and the reaction conditions.<sup>6</sup> Carbonyl cyanide also undergoes Diels-Alder reaction with some conjugated dienes to give dicyanodihydropyrans.<sup>7</sup>

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### 3-CHLOROCYCLOBUTANECARBOXYLIC ACID

(Cyclobutanecarboxylic acid, 3-chloro-)



Submitted by GARY M. LAMPMAN and JAMES C. AUMILLER<sup>1</sup>  
 Checked by G. NELSON and K. B. WIBERG

### 1. Procedure

In a 2-l. three-necked round-bottomed flask equipped with a Trubore stirrer and paddle are placed 172.8 g. (1.2 moles) of 1,1-cyclobutanedicarboxylic acid (Note 1) and 1500 ml. of benzene. The mixture is stirred and heated at reflux, and 200 ml. of benzene and benzene-water azeotrope is removed by distillation to ensure anhydrous conditions. The flask is then fitted with an addition funnel and a reflux condenser to which is attached a drying tube. Stirring and heating are continued, and over a 40-minute period, 170 g. (102 ml., 1.26 moles) of sulfuryl chloride (Note 2) is added from the funnel while 4.0 g. of benzoyl peroxide (Note 3) is simultaneously added in small portions through the top of the condenser. There is a short induction period, and then hydrogen chloride and sulfur dioxide are evolved. After the addition is complete, heating at reflux is maintained for 22 hours. The solid is dissolved after 1 hour, leaving a light brown solution. After the heating period is

complete, the benzene is removed by distillation, and the residue heated to 190–210° for 45 minutes in order to effect decarboxylation. The black residue is transferred to a small flask and distilled under vacuum through a 6-cm. Vigreux column. After a fore-run of about 25–30 g. (Note 4), 65–79 g. (40–49%) of *cis*- and *trans*-3-chlorocyclobutanecarboxylic acid is collected as a light yellow liquid, b.p. 131–137° (15 mm.)  $n^{24}_D$  1.4790 (Note 5). A black residue is present in the distillation flask.

## 2. Notes

1. Diethyl 1,1-cyclobutanedicarboxylate is prepared by the method of Mariella and Raube.<sup>2</sup> The diester is isolated in 55% yield, b.p. 111–114° (16 mm.). The diester can be saponified by the method of Heisig and Stodola,<sup>3</sup> but omitting the barium chloride step, to give the diacid. This material upon recrystallization from ethyl acetate gives the diacid in high purity. The diacid may also be purchased from Aldrich Chemical Company, Inc.

2. Eastman Organic Chemicals or Matheson Coleman and Bell practical grade material was distilled before use. Since hydrogen chloride and sulfur dioxide are evolved, the preparation should be carried out in an efficient hood.

3. Eastman Organic Chemicals white label material was used.

4. The fore-run contains cyclobutanecarboxylic acid and 3-chlorocyclobutanecarboxylic acid, b.p. 100–130° (15 mm.)  $n^{24}_D$  1.4623. The presence of cyclobutanecarboxylic acid indicates that some of the diacid was not chlorinated. Attempts were made to reduce the amount of unchlorinated product by increasing the amount of sulfuryl chloride. Instead, this increased the amount of a dichlorinated impurity which is difficult to separate from the desired product.

5. The product is analyzed by gas chromatography at 190° on a Beckman GC-2 chromatograph equipped with a 180 cm.  $\times$  6 mm. column (Beckman 17449) containing 42/60 Johns-Manville C-22 firebrick coated with Dow-Corning 550 silicone

oil. The retention times are 8 and 9 minutes for the *trans* and *cis* compounds, respectively.

## 3. Discussion

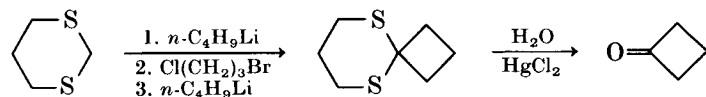
3-Chlorocyclobutanecarboxylic acid has been prepared from the rather inaccessible 3-hydroxy-1,1-cyclobutanedicarboxylic acid.<sup>4</sup> The related 3-bromocyclobutanecarboxylic acid has also been prepared by a long synthetic scheme of eight steps.<sup>5</sup> The present method, based upon the procedure of Nevill, Frank, and Trepka,<sup>6</sup> affords the 3-chloro acid in high yield in one step. Thus this method provides a compound which cannot be easily made by other methods.

The use of sulfuryl chloride for free radical chlorination of aliphatic carboxylic acids gives mixtures of positional isomers.<sup>7</sup> However, with the cyclobutane ring, the attack is much more selective. The present method provides a procedure for free radical halogenation of a cyclobutane ring.

The conversion of 3-chlorocyclobutanecarboxylic acid to 1-bromo-3-chlorocyclobutane is described in *Organic Syntheses*.<sup>8</sup>

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**CYCLIC KETONES FROM  
1,3-DITHIANE: CYCLOBUTANONE**



Submitted by D. SEEBACH and A. K. BECK<sup>1</sup>

Checked by JOSE F. PAZOS and RICHARD E. BENSON<sup>2</sup>

### 1. Procedure

**A. 5,9-Dithiaspiro[3.5]nonane.** A dry 2-l. one-necked round-bottomed flask containing a magnetic stirring bar (Note 1) is flushed with dry nitrogen (Note 2), and 1.25 l. of dry tetrahydrofuran (Note 3) and 50 g. (0.417 mole) of 1,3-dithiane (Note 4) are added. The flask is quickly equipped with a three-way stopcock bearing a standard tapered joint, a rubber septum, and a nitrogen inlet, as shown in Figure 1 (Note 5). The solution is stirred with an efficient magnetic stirrer and cooled to an external temperature of  $-20^{\circ}$  with a dry ice-methanol bath. A 3% excess (total of 0.430 mole) of 1.5–2.5*M* *n*-butyllithium in *n*-hexane (Note 6) is added through the rubber septum by means of a syringe. The bath temperature is kept between  $-10^{\circ}$  and  $-20^{\circ}$  for 2 hours, and then the temperature of the bath is reduced to  $-75^{\circ}$  (Note 7). Sixty-five and five-tenths grams (44.5 ml., 0.417 mole) of 1-bromo-3-chloropropane (Note 8) is added by means of a syringe during 10 minutes. The temperature of the bath is raised to  $-30^{\circ}$  over a 2-hour period by gradually replacing the cold methanol with warm methanol. The bath is removed and stirring is continued until the reaction flask is at room temperature (Note 9). The flask is again cooled to  $-75^{\circ}$  (Note 7) and 0.44 mole of *n*-butyllithium in *n*-hexane (Note 6) is added by means of a syringe during 10 minutes. After the addition is complete, the temperature of the reaction flask is allowed to rise to room temperature overnight (Note 10). The solvent is removed from the product by distillation at  $50^{\circ}$

by means of a rotary evaporator attached to a water aspirator. Three hundred milliliters of water and 500 ml. of ether are added to the product in the flask, the ether layer is separated, and the aqueous layer is washed again with 500 ml. of ether. The organic layers are combined, washed with 200 ml. of water, and dried over 10 g. of anhydrous potassium carbonate. The ether is removed by distillation to yield about 75 g. of crude product. Distillation through a packed column gives 44–57 g.

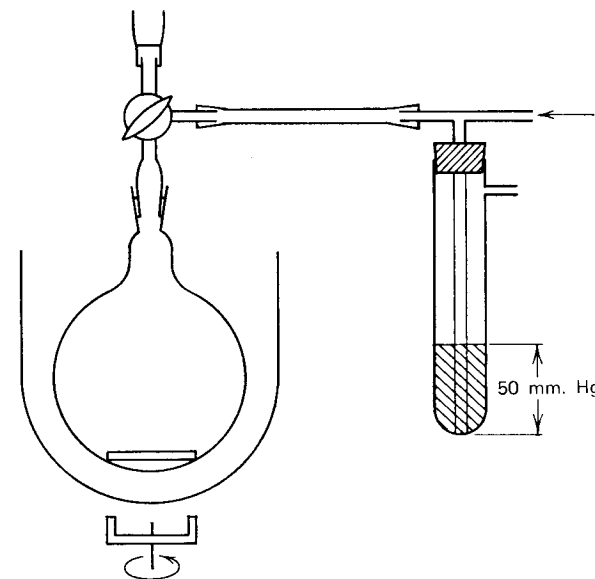


Figure 1

(65–84%) of 5,9-dithiaspiro[3.5]nonane, b.p.  $65-75^{\circ}$  (1 mm.),  $n_D^{20}$  1.5700. This product is of sufficient purity for Part B (Note 11).

**B. Cyclobutanone.** A 2-l. three-necked flask is fitted with an efficient mechanical stirrer and a water-cooled condenser assembled for downward distillation to which is attached a 250-ml. receiver with a side arm. Two cold traps are attached consecutively to the distillation apparatus as shown in Figure 2 (Note 12). The receiver is immersed in an ice-water bath, and the traps are immersed in dry ice-acetone. To the flask is

added 45 g. (0.28 mole) of 5,9-dithiaspiro[3.5]nonane, 900 ml. of triethyleneglycol, and 150 ml. of water. Stirring is begun, and 163 g. (0.6 mole) of mercuric chloride (Note 13) and 51.5 g. (0.3 mole) of cadmium carbonate (Note 13) are added. A nitrogen inlet tube reaching to the bottom of the flask is inserted into the third neck of the flask, and nitrogen is introduced at approximately 50 cc. per minute. The reaction flask is heated to 90° in an oil bath, and the temperature is slowly increased to 110° over a 2–3 hour period. Water and cyclobutanone are carried into the receivers. The water in the receiving flask is saturated with sodium chloride, and the resulting solution is transferred to a separatory funnel. The flask is

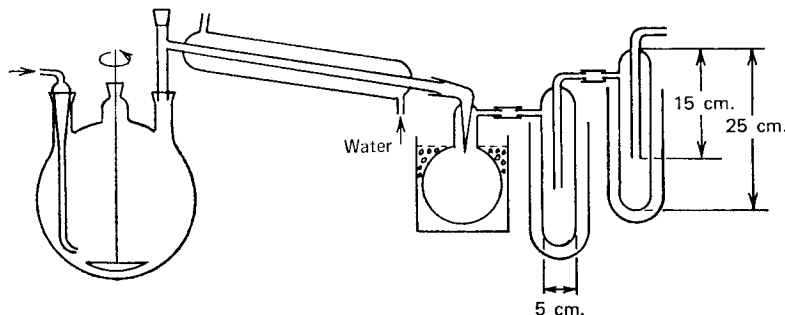


Figure 2

rinsed with 25 ml. of methylene chloride, and this solution is used for an initial washing of the aqueous solution. The aqueous solution is shaken three additional times with 25-ml. portions of methylene chloride. The methylene chloride solutions are combined and added to the traps to dissolve cyclobutanone. The resulting solution is transferred to a 250-ml. flask, the traps are rinsed with a small amount of methylene chloride, and the rinse is combined with the original solution. The methylene chloride solution is dried over 5 g. of anhydrous sodium sulfate, filtered, and the solvent is removed by distillation through a 20-cm. helix-packed vacuum-insulated column. The product is transferred to a 25-ml. flask, 5 ml. of mesitylene is added, and

the product is distilled through a spinning-band column. The fraction boiling at 95–100° is collected. The yield of cyclobutanone is 12–15.8 g. (60–81%) (Note 14).

## 2. Notes

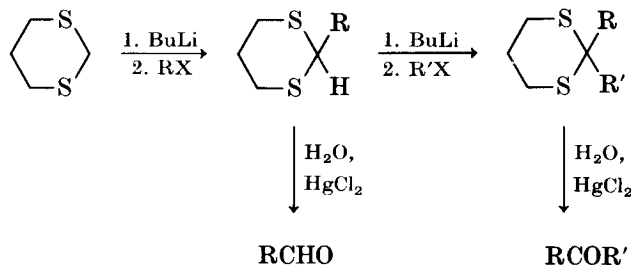
1. Efficient stirring is required throughout the reaction.
2. If available, argon is preferable to nitrogen because of its higher density.
3. The checkers used reagent-grade tetrahydrofuran (available from Fisher Scientific Company) from a freshly opened bottle. The submitters used tetrahydrofuran purified by distillation from lithium aluminum hydride. See *Org. Syn.*, **46**, 105 (1966), for warning regarding purification of tetrahydrofuran.
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5. During the entire reaction sequence a positive pressure of approximately 50 mm. of nitrogen is maintained against the atmosphere with a mercury bubbler.
6. The titer of the solution should be determined prior to use. The checkers used product available from Foote Mineral Company.
7. Only a slight excess of dry ice should be added.
8. Available from Eastman Organic Chemicals. The product was distilled prior to use, b.p. 140–142°.
9. Approximately 2 hours is required.
10. The submitters have found that the ring closure reaction is essentially complete by the time the temperature reaches –20°.
11. Gas chromatography analysis using a column containing 20% silicone DC 200 on Gas Chrom Z at 160° showed the product to be 96% pure.
12. The traps are attached in a reverse manner. The diameter of the inner tubing is 1.5 cm.
13. Anhydrous practical grade reagents were used.
14. The infrared spectrum (neat) shows strong absorption at 1775 cm.<sup>-1</sup>. The purity of the product is greater than 95% as established by gas chromatography on a 4-ft. column containing 20% silicone DC 200 on Gas Chrom Z at 50°. The n.m.r.



spectrum (carbon tetrachloride solution, internal tetramethylsilane reference) shows a pentet at 1.83 p.p.m. ( $J = 8$  Hz.) and a triplet at 3.01 p.p.m. ( $J = 8$  Hz.) in a ratio 1:2, respectively.

### 3. Discussion

The best large-scale preparation of cyclobutanone is the reaction of diazomethane with ketene.<sup>2</sup> It requires a ketene generator and implies handling of large quantities of the potentially hazardous diazo compound. A more frequently used method for the preparation of cyclobutanone starts from pentaerythritol, the final step being the oxidative degradation of methylenecyclobutane,<sup>3,4</sup> which can also be prepared from other precursors.<sup>5</sup> A general survey of all methods used to obtain cyclobutanone has been published.<sup>6,7</sup>

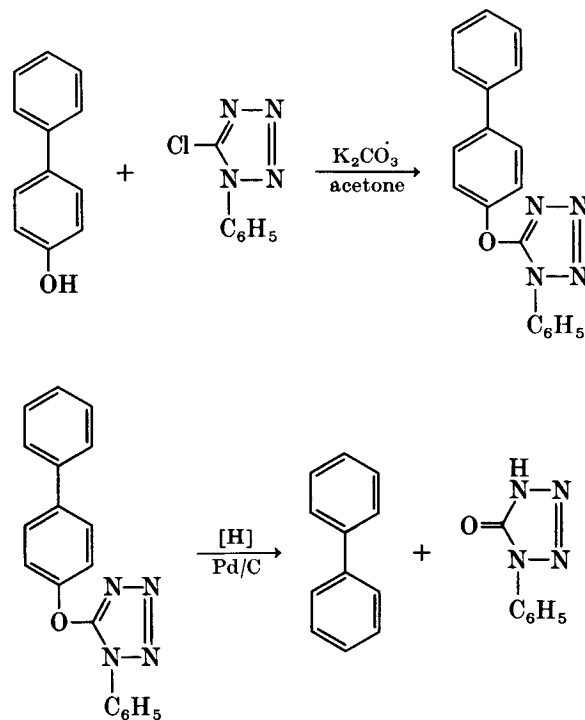


The procedure described here is an example of the use of the dithiane method<sup>8</sup> for the preparation of ketones. The reactions appear to be general, and the yields are satisfactory. The dithiane method can be successfully applied to the synthesis of rings containing up to seven carbon atoms with a slight modification<sup>9,10</sup> of the procedure above. The synthesis of larger rings may require high dilution methods.<sup>9</sup>

Aldehydes and open-chain ketones are also available from dithiane.<sup>9</sup> Carbonyl compounds with high optical activity<sup>9</sup> have been synthesized including those that undergo facile racemization. An extensive review covering all applications of this reaction up to June 1969 has been authored by one of the submitters.<sup>9</sup> Methods and limitations for the preparation of silyl ketones<sup>11</sup> ( $\text{R}_3\text{SiCOR}$ ) and germanyl ketones ( $\text{R}_3\text{GeCOR}$ ) have been described.<sup>12</sup>

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**DEHYDROXYLATION OF PHENOLS;  
HYDROGENOLYSIS OF PHENOLIC ETHERS:  
BIPHENYL**



Submitted by WALTER J. MUSLINER and JOHN W. GATES, JR.<sup>1</sup>  
Checked by D. ROBERT COULSON and RICHARD E. BENSON

### 1. Procedure

**A. Preparation of the Phenolic Ether: *p*-(1-Phenyl-5-tetrazolyloxy)biphenyl.** In a 1-l. round-bottomed flask fitted with an efficient condenser is placed a magnetic bar for stirring. Seventeen grams (0.1 mole) of *p*-phenylphenol, 18.1 g. (0.1 mole) of 1-phenyl-5-chlorotetrazole (Note 1), 27.6 g. (0.2 mole) of anhydrous potassium carbonate, and 250 ml. of acetone are added to the flask, and the mixture is stirred and heated under

reflux for 18 hours (Note 2). Water (250 ml.) is added to the hot mixture to give a clear solution that is chilled in ice. After 1 hour, the product is collected by filtration and dried in air. The crude product (32–33 g., m.p. 151–153°) is dissolved in 250 ml. of hot ethyl acetate, and the solution is filtered while hot to free it from a small amount of insoluble material. The white crystals of *p*-(1-phenyl-5-tetrazolyloxy)biphenyl that separate on cooling in ice weigh 25 g., m.p. 150–153°. An additional 2–3 g. of product is recovered from the filtrate by concentration to 125 ml. The total yield is 27–28 g. (86–89%).

**B. Hydrogenolysis of the Phenolic Ether: Biphenyl.** To a solution of 10 g. (0.032 mole) of the product from Part A in 200 ml. of benzene is added 2 g. of 5% palladium-on-charcoal, and the mixture is shaken with hydrogen in a Parr apparatus at 40 p.s.i. and 35–40° for 8 hours (Note 3). The mixture is filtered, and the insoluble residue is washed with three 100-ml. portions of hot ethanol (Note 4). The filtrates are combined, and the solvent is removed by means of a rotary evaporator at 60° (12 mm.) to leave a solid residue. The product is dissolved in 100 ml. of benzene, and 100 ml. of 10% sodium hydroxide solution is added. The mixture is shaken, and the layers are separated. The aqueous layer is extracted with 100 ml. of benzene, and the original benzene layer is washed with 100 ml. of water (Note 5). The benzene solutions are combined and dried over magnesium sulfate. Removal of the benzene by distillation yields 4.0–4.7 g. (82–96%) of biphenyl as a white powder, m.p. 68–70° (Note 6). The infrared spectrum is identical with that of an authentic sample, and a purity of at least 99.5% was indicated by gas chromatography analysis.

### 2. Notes

1. *p*-Phenylphenol and 1-phenyl-5-chlorotetrazole were obtained from Eastman Organic Chemicals.

2. A reflux period of 18 hours was chosen because it represents an overnight reaction time; the reaction is essentially completed in 8 to 10 hours.

3. The hydrogenolysis can also be carried out in ethanol or

tetrahydrofuran. An amount of catalyst equivalent to 10–20% by weight of tetrazolyl ethers is most satisfactory for this reaction. Platinum oxide also catalyzes this hydrogenolysis.

4. A large portion of 1-phenyl-5-tetrazolone (and a small amount of biphenyl) remains mixed with and adsorbed to the catalyst and is removed by the ethanol treatment.

5. 1-Phenyl-5-tetrazolone can be recovered from the combined aqueous solutions by acidification with dilute hydrochloric acid. The yield is 4.2–4.7 g. (82–92%), m.p. 190–191°.

6. Benzoxazolyl ethers can also be used in this reaction sequence but an amount of catalyst equivalent to 20–40% by weight of ether is necessary in the hydrogenolysis step. 2-Chlorobenzoxazole is available from Eastman Organic Chemicals.

### 3. Discussion

The preparation is essentially that described by the submitters<sup>2</sup> and is cited as an example of this general procedure for replacement of phenolic hydroxyl groups by hydrogen.

The reaction sequence, which involves the conversion of the phenolic hydroxyl groups to a phenyltetrazolyl ether (see Note 6) followed by reduction to effect removal of the phenolic hydroxyl group, illustrates a mild, efficient, general, and convenient procedure. It has been applied successfully by the submitters<sup>2</sup> to a variety of substituted phenols, as shown in Table I.

Phenols having a variety of substituents including alkyl, alkoxyl, aryl, amino, and carbalkoxyl have been successfully converted to the desired product in good yield. The only limitation yet found is in the hydrogenolysis of the halogen-carbon bond. Thus *p*-chlorophenol was converted to benzene using this procedure.

Other procedures include zinc-dust distillation, not generally useful except for exhaustive degradation of phenols to hydrocarbons, and various sodium and liquid ammonia cleavages of phenol ethers.<sup>3–7</sup> These latter reactions lack generality and are often unpredictable. They require conditions too harsh for

TABLE I  
HYDROGENOLYSIS OF PHENOLIC ETHERS

Substituted Phenol	Yield of Tetrazolyl Ether, %	Hydrogenolysis Time, hours	Hydrogenolysis	
			Product	Yield, %
Guaiacol	94	15	Anisole	86 <sup>a</sup>
<i>m</i> -Methoxyphenol	95	16	Anisole	85 <sup>a</sup>
<i>p</i> -Methoxyphenol	97	6	Anisole	83 <sup>a</sup>
<i>o</i> -Phenylphenol	98	8	Biphenyl	82
<i>p</i> -Aminophenol	86	9	Aniline	46 <sup>b</sup>
<i>p</i> -Carbethoxyphenol	91	16	Ethyl benzoate	89 <sup>a</sup>
Thymol	93	15	<i>p</i> -Cymene	72 <sup>a</sup>
1-Naphthol	88	7	Naphthalene	50
2-Naphthol	94	17	Naphthalene	65
<i>p</i> -Chlorophenol	92	18	Benzene <sup>c</sup>	70 <sup>a</sup>

<sup>a</sup> Filtered solution analyzed directly by gas chromatography with toluene as internal standard.

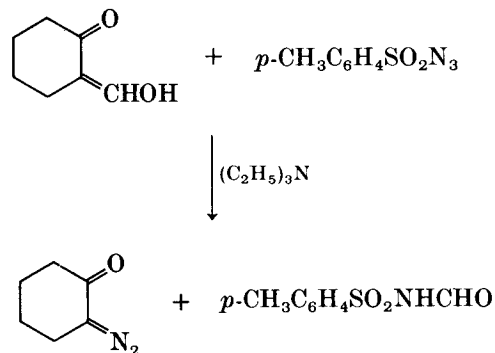
<sup>b</sup> Isolated as the hydrochloride salt.

<sup>c</sup> From hydrogenolysis of carbon-chlorine bond.

certain aromatic substituents, and the yields are frequently low.

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**2-DIAZOCYCLOALKANONES:  
2-DIAZOCYCLOHEXANONE**



Submitted by MANFRED REGITZ, JÖRN RÜTER,  
and ANNEMARIE LIEDHEGENER<sup>1</sup>  
Checked by JOHN D. FENWICK and PETER YATES

### 1. Procedure

*Caution: 2-Diazocyclohexanone may explode, especially on being heated. The workup and distillation should be carried out in a fume hood behind a safety shield.*

In a 2-l. wide-necked Erlenmeyer flask are mixed 66.2 g. (0.525 mole) of 2-(hydroxymethylene)cyclohexanone (Note 1), 400 ml. of methylene chloride, and 106 g. (1.05 moles) of triethylamine (Note 2). The flask is cooled in an ice-salt bath at  $-12$  to  $-15^{\circ}$ , and 98.0 g. (0.500 mole) of *p*-toluenesulfonyl azide (Note 3) is added with vigorous mechanical stirring over a period of approximately 1 hour, at such a rate that the temperature of the reaction mixture does not rise above  $-5^{\circ}$ . Stirring is continued for an additional 2 hours as the cooling bath melts. A solution of 30.8 g. (0.55 mole) of potassium hydroxide in 400 ml. of water is added, and the mixture is stirred for 15 minutes at room temperature. The resulting emulsion is placed in a 2-l. separatory funnel, the methylene chloride layer is separated after the emulsion has broken, and the aqueous alcoholic layer is

washed with two 100-ml. portions of methylene chloride. The combined methylene chloride solutions are washed with a solution of 2.8 g. of potassium hydroxide in 200 ml. of water, and then with 200 ml. of water, and dried over anhydrous sodium sulfate (Note 4). The solvent is removed on a rotary evaporator at  $35^{\circ}$  (15 mm.) until the weight of the residue is constant. The yield of yellow-orange 2-diazocyclohexanone is 51.5–59.0 g. (83–95%) (Note 5). Distillation with magnetic stirring (Note 6) of 20 g. of this crude product from a hot-water bath at  $80^{\circ}$  gave 17.0 g. of yellow-orange liquid, b.p.  $46^{\circ}$  (0.1 mm.) or  $60^{\circ}$  (0.4 mm.) (Note 7). The infrared spectrum (liquid film) has a strong band at  $2083\text{ cm.}^{-1}$  attributable to the diazo function.

### 2. Notes

1. 2-(Hydroxymethylene)cyclohexanone was prepared from cyclohexanone<sup>2</sup> and was freshly distilled before use.

2. Freshly distilled; b.p.  $88.5$ – $90.5^{\circ}$ .

3. *p*-Toluenesulfonyl azide was prepared from *p*-toluenesulfonyl chloride and sodium azide.<sup>3</sup> The submitters found that when somewhat less than the stoichiometric quantity of *p*-toluenesulfonyl azide is used, 2-diazocyclohexanone is obtained free of azide; the excess 2-(hydroxymethylene)cyclohexanone is readily removed in the alkaline workup. The crude product obtained by the checkers, however, contained *p*-toluenesulfonyl azide (Note 5).

4. The basic aqueous solution on acidification with 6*N* hydrochloric acid gives *N*-formyl-*p*-toluenesulfonamide in almost quantitative yield. Crystallization from benzene gave crystals, m.p.  $101$ – $102^{\circ}$  (lit.<sup>4</sup>  $102$ – $103^{\circ}$ ).

5. The submitters found that this product gave a single spot on thin-layer chromatography (Note 8), and that it can be used for most preparative purposes without distillation. The checkers found by n.m.r. spectroscopy that the product contained *p*-toluenesulfonyl azide (*ca.* 5%) and triethylamine.

6. If the distillation is carried out with a capillary leak, thus in the presence of air, decomposition of the diazo compound

occurs. The checkers found that distillation on a larger scale led to extensive decomposition.

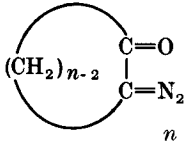
7. The distillation is not carried to completion because of the resulting danger of explosion. It is carried out with the usual safety precautions (safety shield), although no explosion has yet occurred.

8. Thin-layer chromatography was carried out on DC-Fertigplatte Merck Kieselgel F<sub>254</sub> supplied by Firma Merck AG, 61 Darmstadt, Germany. For the solvent system methylene chloride/methanol (97/3) the product has an *R<sub>f</sub>* value of 0.45.

### 3. Discussion

In addition to previously described syntheses<sup>4,5</sup> by diazo group transfer with deformylation,<sup>6</sup> 2-diazocyclohexanone has been prepared by two variants of this method. In one, the reaction of 2-(hydroxymethylene)cyclohexanone with *p*-toluenesulfonyl azide is carried out in ether/diethylamine, and an enamine is assumed to be formed as an intermediate;<sup>7</sup> in the other, the sodium salt of the hydroxymethylene compound was treated with the lithium salt of *p*-carboxybenzenesulfonyl azide

TABLE I  
PREPARATION OF 2-DIAZOCYCLOALKANONES

	Boiling Point or [Melting Point], °C.	Yield, %
<i>n</i>		
5	34–37 (0.8 mm.)	98
7	62 (0.4 mm.)	83
8	<sup>a</sup>	87
9	<sup>a</sup>	73
10	[54–55]	81
11	<sup>b</sup>	79
12	[42–43]	57

<sup>a</sup> Liquid, purified by crystallization from ether at –60°.

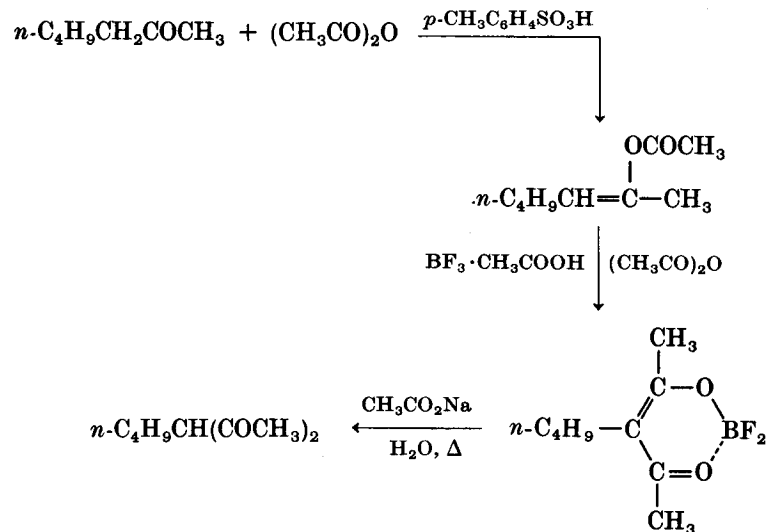
<sup>b</sup> Liquid, purified by crystallization from ethanol at –20°.

in ether/tetrahydrofuran.<sup>8</sup> Its preparation from 1,2-cyclohexanedione mono-*p*-toluenesulfonylhydrazone was described earlier.<sup>9</sup>

2-Diazocycloalkanones with five- to twelve-membered rings can be synthesized by the present procedure in good yields (Table I).<sup>4</sup> Diazo transfer with deformylation can also be used for the preparation of bicyclic  $\alpha$ -diazo ketones.<sup>10,11</sup> A related procedure involving reaction of the sodium salt of an  $\alpha$ -(hydroxymethylene)-ketone with *p*-toluenesulfonyl azide in ethanol has been applied to the synthesis of diazoalkyl ketones,  $\alpha$ -diazo aldehydes, and  $\alpha$ -diazo carboxylic esters.<sup>12</sup>

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β-DIKETONES FROM METHYL ALKYL KETONES:  
3-*n*-BUTYL-2,4-PENTANEDIONE



Submitted by CHUNG-LING MAO<sup>1</sup> and CHARLES R. HAUSER<sup>1,2</sup>  
Checked by DAVID G. MELILLO and HERBERT O. HOUSE

### 1. Procedure

A mixture of 28.6 g. (0.25 mole) of 2-heptanone (Note 1), 51.0 g. (0.50 mole) of acetic anhydride (Note 2), and 1.9 g. (0.01 mole) of *p*-toluenesulfonic acid monohydrate (Note 3) contained in a stoppered 500-ml. round-bottomed flask equipped with a magnetic stirrer is stirred at room temperature for 30 minutes. Then 55 g. (0.43 mole) of the solid 1:1 boron trifluoride-acetic acid complex (Note 4) is added; some heat is evolved during this addition. The resulting amber-colored solution is stirred in the stoppered flask at room temperature for 16-20 hours (Note 5), and then a solution of 136 g. (1.00 mole) of sodium acetate trihydrate (Note 6) in 250 ml. of water is added. After the flask has been fitted with a reflux condenser, the reaction mixture is heated at reflux for 3 hours and then cooled,

and the product is extracted with three 100-ml. portions of petroleum ether (b.p. 30–60°). The combined organic extracts are washed successively with aqueous 5% sodium bicarbonate and with saturated aqueous sodium chloride. After the petroleum ether solution has been dried over anhydrous calcium sulfate (Drierite), the solvent is removed with a rotary evaporator, and the residual oil is distilled. 3-*n*-Butyl-2,4-pentanedione is collected as a colorless liquid, b.p. 84–86° (6 mm.),  $n_{\text{D}}^{25}$  1.4422–1.4462 (Note 7). The yield is 25–30 g. (64–77%).

### 2. Notes

1. 2-Heptanone, obtained from Eastman Organic Chemicals, was distilled before use, b.p. 145–147°.

2. Acetic anhydride purchased from Merck & Co., Inc. was fractionally distilled and the fraction, b.p. 139–141°, was used.

3. *p*-Toluenesulfonic acid monohydrate was obtained from Eastman Organic Chemicals and used without purification.

4. The submitters employed 75 g. (0.5 mole) of the liquid 1:2 boron trifluoride-acetic acid complex obtained from Harshaw Chemical Company. Since the checkers were unable to obtain this complex from a commercial source, they prepared the solid 1:1 complex following published directions.<sup>3,4</sup> A 2-l. three-necked flask is fitted with a mechanical stirrer, a gas outlet tube, and a gas inlet tube extending to the bottom of the flask. A solution of 230 ml. of acetic acid in 750 ml. of 1,2-dichloroethane is added to the flask and a stream of boron trifluoride gas is passed through the reaction flask while the solution is stirred and cooled with an ice bath. After approximately 1 hour, when the mixture is saturated, the addition of boron trifluoride is stopped and the insoluble 1:1 boron trifluoride-acetic acid complex is rapidly collected on a filter, washed with 200 ml. of 1,2-dichloroethane, and transferred to a dry stoppered container. Since this solid complex tends to liquefy partially on storage, portions to be used in this preparation should be washed with 1,2-dichloroethane immediately prior to use. The amount of catalyst obtained is sufficient to perform this preparation several times.

5. A longer reaction time gives similar results.

6. Sodium acetate trihydrate was obtained from Eastman Organic Chemicals.

7. On a gas chromatographic column packed with SE-30 silicone gum on Chromosorb P and heated to 150°, the product exhibits a single peak with a retention time of 12.3 minutes; under the same conditions the peak for 2-heptanone has a retention time of 4.4 minutes. The product, which is partially enolic, has infrared bands (carbon tetrachloride solution) at 1725(sh), 1695, and 1605  $\text{cm}^{-1}$  with an ultraviolet maximum (95% ethanol) at 288  $\text{m}\mu$  ( $\epsilon$  2560) and n.m.r. peaks (carbon tetrachloride solution) at 16.50 (singlet, *ca.* 0.3H, enolic OH), 3.57 (triplet,  $J = 7$  Hz., *ca.* 0.7H, COCHCO), 2.10 (singlet, 6H, COCH<sub>3</sub>) and 0.7–2.0 p.p.m. (multiplet, 9H, aliphatic CH). The mass spectrum exhibits a molecular ion at  $m/e$  156 with abundant fragment peaks at  $m/e$  100, 71, 58, 44, and 43 (base peak).

### 3. Discussion

This procedure for the acetylation of methyl alkyl ketones to form  $\beta$ -diketones is a modification<sup>5</sup> of an earlier procedure, which used boron trifluoride gas as the catalyst.<sup>6</sup> 3-*n*-Butyl-2,4-pentanedione has also been prepared by the acetylation of 2-heptanone catalyzed with boron trifluoride gas,<sup>7</sup> by the thermal rearrangement of the enol acetate of 2-heptanone,<sup>7</sup> and by the alkylation of the potassium enolate of 2,4-pentanedione with *n*-butyl bromide.<sup>8</sup>

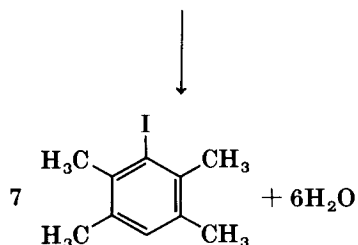
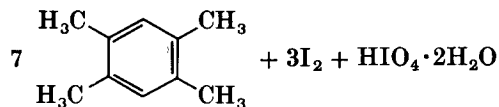
In this procedure, the ketone is first converted to its enol acetate by reaction with acetic anhydride in the presence of a proton acid. Since this enol acetylation is performed under equilibrating conditions, the more stable enol acetate (usually the more highly substituted isomer) is produced. Acetylation of this enol acetate, catalyzed by the Lewis acid boron trifluoride, usually leads to the formation of the enol acetate of a  $\beta$ -diketone which is cleaved by boron trifluoride to form acetyl fluoride and the borofluoride complex of the  $\beta$ -diketone. Thus, this procedure offers a convenient and general synthetic route

to 3-substituted-2,4-pentanediones.<sup>5</sup> The acylation of 2-butanone to give 3-methyl-2,4-pentanedione (48%); 2-pentanone to give 3-ethyl-2,4-pentanedione (57%); phenylacetone to give 3-phenyl-2,4-pentanedione (68%); and 3-methyl-2-butanone to give 3,3-dimethyl-2,4-pentanedione (40–48%) has been reported by the submitters.

A similar acetylation procedure (without *p*-toluenesulfonic acid) has been employed to prepare other  $\beta$ -diketones.<sup>5</sup> As examples, cyclohexanone was converted to 2-acetylcyclohexanone (73%); cyclopentanone yielded 2-acetylcyclopentanone (80%); 3-pentanone yielded 3-methyl-2,4-hexanedione (81%); dibenzyl ketone yielded 1,3-diphenyl-2,4-pentanedione (72%), and acetophenone gave benzoylacetone (70%).

1. Department of Chemistry, Duke University, Durham, North Carolina 27706.
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# DIRECT IODINATION OF POLYALKYLBENZENES: IODODURENE

Submitted by H. SUZUKI<sup>1</sup>

Checked by ROBERT E. IRELAND and ROBERT CZARNY

## 1. Procedure

Into a 200-ml. three-necked flask equipped with a reflux condenser, a thermometer, a glass stopper, and a magnetic stirring bar are introduced 13.4 g. (0.1 mole) of durene (Note 1), 4.56 g. (0.02 mole) of periodic acid dihydrate, and 10.2 g. (0.04 mole) of iodine. To this mixture is then added a solution of 3 ml. of concentrated sulfuric acid and 20 ml. of water in 100 ml. of glacial acetic acid. The resulting purple solution is heated at 65–70° with stirring for approximately 1 hour until the color of iodine disappears. The reaction mixture is then diluted with approximately 250 ml. of water, and the white-yellow solid that separates (Note 2) is collected on a Büchner funnel and washed three times with 100-ml. portions of water. The product is dissolved in a minimum amount of boiling acetone (about 125 ml. is required); the solution is cooled to room temperature and subsequently stored overnight in a refrigerator. The product is collected by rapid filtration through a Büchner funnel. The yield of iododurene in the form of colorless fine needles is 20.8–22.6 g. (80–87%), m.p. 78–80°.

## 2. Notes

1. Durene (m.p. 79–80°), prepared according to the procedure in *Org. Syn.*, Coll. Vol. 2, 248 (1943), was used by the submitter. Commercially available durene that also melted at 79–80° after purification by the *Organic Syntheses* procedure above was used by the checkers.

2. Some crystals of iododurene that have formed during the heating period tend to take on a purple coloration because of occluded iodine. This impurity is readily removed by the recrystallization procedure.

## 3. Discussion

The present procedure is the most convenient method for preparation of mono- or diiodo derivatives from various polyalkylbenzenes in high yields.<sup>2</sup> Thus 5-*t*-butyl-1,3-dimethylbenzene gives 4-*t*-butyl-2,6-dimethyliodobenzene in 90% yield and 4-*t*-butyl-1,2-dimethylbenzene gives 5-*t*-butyl-2,3-dimethyliodobenzene in 81% yield. 5-*t*-Butyl-1,2,3-trimethylbenzene, 1,2,4,5-tetraisopropylbenzene, and *p*-di-*t*-butylbenzene have also been successfully converted to the corresponding monoiodo derivatives by this method. Diiodo derivatives have been prepared from *o*-xylene, *p*-xylene, durene, and prehnitene by use of excess reagent. Shorter reaction times and higher degree of purity of the product are assured by the use of periodic acid as oxidizing agent. However, the preparation of the more highly iodinated alkylbenzenes by this procedure is difficult, and the Jacobsen reaction for the disproportionation of diiodo compounds by the action of sulfuric acid is preferred.<sup>3</sup>

Iododurene has been prepared by treatment of durene either with iodine and mercuric oxide,<sup>4</sup> or with sulphur iodide and nitric acid.<sup>5</sup>

1. Department of Chemistry, Kyoto University, Kyoto, Japan.

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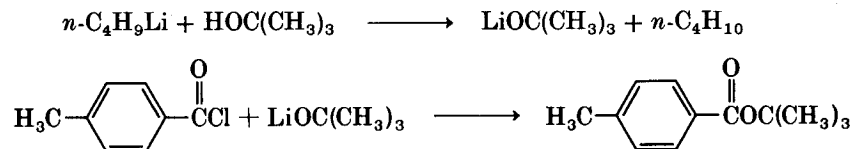
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# ESTERIFICATION OF HINDERED ALCOHOLS: *t*-BUTYL *p*-TOLUATE



Submitted by G. P. CROWTHER,<sup>1</sup> E. M. KAISER,<sup>2</sup>  
R. A. WOODRUFF,<sup>2</sup> and C. R. HAUSER<sup>3</sup>  
Checked by A. BROSSI, R. A. LEMAHIEU, and P. LASALLE

## 1. Procedure

In a 200-ml. one-necked round-bottomed flask fitted with a Claisen adapter with a condenser and addition funnel is placed a magnetic stirring bar and 50 ml. of *t*-butanol (Note 1). Under nitrogen, 22.6 ml. of a solution of approximately 1.55*M* (0.035 mole) *n*-butyllithium in hexane (Note 2) is added slowly from a syringe (Note 3) to give a turbid reaction mixture. A water bath is used to keep the mixture near room temperature. After stirring for 15 minutes, a solution of 5.42 g. (0.035 mole) of *p*-toluoyl chloride (Note 4) in 25 ml. of anhydrous ethyl ether (Note 5) is added dropwise to the stirred mixture. The resulting yellow slurry is stirred at room temperature for 15 hours (Note 6). The yellow suspension (Note 7) is transferred with 100 ml. of ethyl ether to a separatory funnel and washed three times with 25-ml. portions of saturated sodium chloride solution. The resulting ether solution is dried over magnesium sulfate. The ether is removed by distillation, and the residual oil distilled under reduced pressure to give a small fore-run (0.10 g.) and 5.31–5.51 g. (79–82%) of *t*-butyl *p*-toluate, b.p. 98–101° (4.2 mm.) (Note 8).

## 2. Notes

1. *t*-Butanol (Eastman Organic Chemicals white label) was dried by distillation from calcium hydride.

2. The solution of 1.55*M* *n*-butyllithium in hexane was obtained from Foote Mineral Company.

3. Formation of the lithium *t*-butoxide in this manner is very exothermic and causes the hexane to boil during addition.

4. *p*-Toluoyl chloride was prepared by treating *p*-toluic acid (Eastman Organic Chemicals white label) with thionyl chloride (Eastman Organic Chemicals white label). The *p*-toluoyl chloride used was distilled, b.p. 48–49° (0.1 mm.).

5. Anhydrous ethyl ether was distilled from lithium aluminum hydride and stored over sodium ribbon prior to use.

6. In one instance an additional 75 ml. of anhydrous ether was added to make the slurry less viscous. The ester was obtained in the same yield in another run after stirring only 30 minutes.

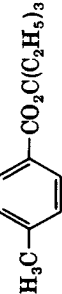
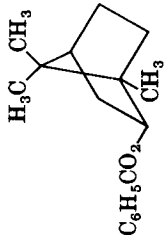


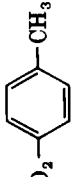

7. The reaction mixture alternatively may be concentrated with a rotary evaporator to remove the excess *t*-butanol. Ethyl ether and water are added, and the mixture transferred to the separatory funnel; the yield of ester is unchanged.

8. With the same procedure *t*-butyl phenylacetate has been prepared in 47% yield.<sup>4</sup> When esters of less common alcohols were prepared, anhydrous ether was used as a solvent instead of excess alcohol. Equivalent amounts of alcohol, *n*-butyllithium, and acid chloride were employed. Thus the triethylcarbinol ester of *p*-toluic acid and the 2,2-diphenylethanol ester of benzoic acid have been prepared in 72 and 70% yields, respectively.

## 3. Discussion

The present procedure<sup>4</sup> is an especially effective method for the synthesis of esters of aromatic acids and hindered tertiary alcohols or of acid-labile alcohols such as 2,2-diphenylethanol. The yields are excellent, and the reaction procedure is simple. The method is illustrated by the preparation of *t*-butyl *p*-toluate, a compound that could not be prepared by a conventional method<sup>5</sup> of esterification involving the acid chloride and *t*-butanol in the presence of dimethylaniline. Examples of esters prepared by this method are illustrated in Table I.

TABLE I  
ESTERS PREPARED BY ALKOXIDE METHODS

Ester	Yield, %	Ester	Yield, %
$C_6H_5CH_2CO_2C(CH_3)_3$	47 <sup>a</sup>	$C_6H_5CO_2CH_2CH(C_6H_5)_2$ $C_6H_5CO_2C(CH_3)_3$ $C_6H_5CO_2CCH_3(C_2H_5)_2$ $C_6H_5CO_2C(C_2H_5)_3$ $CH_3$ $ $ $C_6H_5CO_2CH(t-C_4H_9)$ $C_6H_5CO_2CH_2(t-C_4H_9)$ $C_6H_5CO_2$  $HC\equiv C$ $H_3C$ $CH_3$  $C_6H_5CO_2$	70 <sup>b</sup> 89 <sup>c</sup> 87 <sup>c</sup> 94 <sup>c</sup> 76 <sup>c</sup> 78 <sup>c</sup> 70 <sup>c</sup> 69 <sup>c</sup>
$H_3C$ -  - $CO_2C(C_2H_5)_3$	72 <sup>b</sup>		
$C_6H_5CO_2CH_2$ - 	91 <sup>c</sup>		
$C_6H_5CO_2$ - 	94 <sup>c</sup>	$H_3C$ -  - $SO_3CH_2CH(C_6H_5)_2$	85 <sup>d</sup>
$(CH_3)_3CCO_2C(CH_3)_3$ $(CH_3)_3CCO_2C(C_2H_5)_3$ $C_6H_5CH=CHCO_2C(CH_3)_3$ $C_6H_5CH_2CH_2CO_2C(CH_3)_3$	64 <sup>c</sup> 75 <sup>c</sup> 88 <sup>c</sup> 72 <sup>c</sup>	$(i-C_3H_7)_2CHCO_2C(C_2H_5)_3$ $(t-C_4H_9)CH_2CO_2C(C_2H_5)_3$ $(t-C_4H_9)_2CHCO_2C(C_2H_5)_3$	88 <sup>e</sup> 86 <sup>e</sup> 30 <sup>e</sup>

<sup>a</sup> As described in the accompanying procedure.

<sup>b</sup> As described in the accompanying procedure except ether used as solvent (see Note 8).

<sup>c</sup> Prepared in refluxing tetrahydrofuran with 1.0 equivalent of appropriate alcohol, 1.1 equivalents of *n*-butyllithium, and 1.1 equivalents of acid chloride.<sup>4</sup>

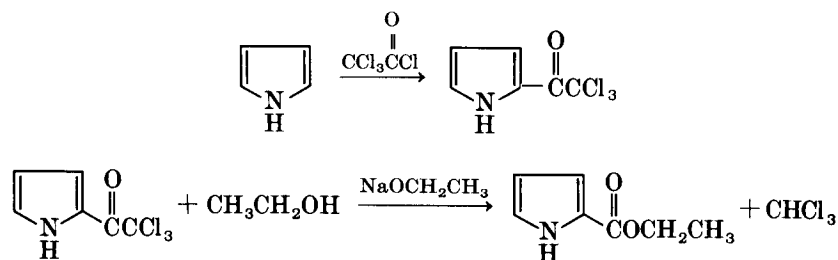
<sup>d</sup> Prepared by adding an equivalent amount of *p*-toluenesulfonyl chloride to a suspension of sodium 2,2-diphenylethoxide in ether.<sup>6</sup>

<sup>e</sup> Prepared by adding 0.50 equivalent of acid chloride to an ether suspension of sodium triethylmethoxide, which was obtained from 0.52 equivalent of sodium amide and 0.55 equivalent of triethylcarbinol.<sup>7</sup>

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2. Chemistry Department, University of Missouri, Columbia, Missouri 65201.
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## ETHYL PYRROLE-2-CARBOXYLATE

(Pyrrole-2-carboxylic acid, ethyl ester)



Submitted by DENIS M. BAILEY, ROBERT E. JOHNSON,  
and NOEL F. ALBERTSON<sup>1</sup>

Checked by A. BROSSI and P. WEHRLI

### 1. Procedure

A. *Pyrrol-2-yl trichloromethyl ketone*. In a 3-l. three-necked round-bottomed flask equipped with a sealed mechanical stirrer, a dropping funnel, and an efficient reflux condenser with a calcium chloride drying tube are placed 225 g. (1.23 moles) of trichloroacetyl chloride and 200 ml. of anhydrous ether. The solution is stirred while 77 g. (1.15 moles) of freshly distilled pyrrole in 640 ml. of anhydrous ether is added over 3 hours (Note 1). The heat of reaction causes the mixture to reflux during the addition. Following the addition, the mixture is stirred for 1 hour, and then 100 g. (0.72 mole) of potassium

carbonate in 300 ml. of water is slowly added through the dropping funnel (Note 2). The layers are separated, and the organic phase is dried with magnesium sulfate, treated with 6 g. of Norit, and filtered. The solvent is removed by distillation on a steam bath, and the residue is dissolved in 225 ml. of hexane. The dark solution is cooled in ice, and the product crystallizes. The tan solid is collected and washed with 100 ml. of cold hexane giving 189–196 g. (77–80%) of the ketone melting at 73–75° (Note 3).

B. *Ethyl pyrrole-2-carboxylate*. In a 1-l. three-necked round-bottomed flask equipped with a sealed mechanical stirrer and powder funnel are placed 1.0 g. of sodium and 300 ml. of anhydrous ethanol. When the sodium is dissolved, 75 g. (0.35 mole) of pyrrol-2-yl trichloromethyl ketone from Part A is added portionwise over a 10-minute period (Note 4). After the addition is complete, the solution is stirred 30 minutes, then concentrated to dryness using a rotary evaporator. The oily residue is partitioned between 200 ml. of ether and 25 ml. of 3*N* hydrochloric acid. The ether layer is separated, and the aqueous layer is washed once with 100 ml. of ether. The ether solutions are combined, washed once with 25 ml. of saturated sodium bicarbonate solution, dried with magnesium sulfate, and concentrated by distillation. The residue is fractionated at reduced pressure to give 44.0–44.5 g. (91–92%) of ethyl pyrrole-2-carboxylate as a pale yellow oil, b.p. 125–128° (25 mm.) (Note 5). The yield based on pyrrole is 70–74%. Upon standing at room temperature the product crystallizes, m.p. 40–42°.

### 2. Notes

1. If the addition time is shortened to 1 hour, the yield is decreased by about 5%.
2. Excessive frothing will occur if the potassium carbonate solution is added too fast.
3. A similar run on a scale 3.3 times as large with a 3-hour addition time gave the ketone in 74% yield.
4. The solution becomes warm during the addition, and the final color of the solution is reddish-brown.

5. A similar run on a scale three times as large gave the ester in 96% yield.

### 3. Discussion

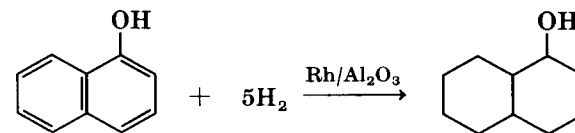
Pyrrole-2-carboxylic acid esters have been prepared from ethyl chloroformate and pyrrolylmagnesium bromide<sup>2</sup> or pyrrolyllithium,<sup>3</sup> by hydrolysis and decarboxylation of dimethyl pyrrole-1,2-dicarboxylate followed by re-esterification of the 2-acid<sup>4</sup> and by oxidation of pyrrole-2-carboxaldehyde followed by esterification with diazomethane.<sup>4</sup>

Methods of acylating pyrrole similar to the present one have been reported using oxalyl chloride,<sup>5</sup> trifluoroacetic anhydride,<sup>6</sup> carbamic acid chloride,<sup>7</sup> and trichloroacetyl chloride.<sup>8</sup> In the last preparation, it was necessary to separate the product from highly colored by-products by alumina chromatography. Pyrrol-2-yl trichloromethyl ketone has also been prepared by the interaction of pyrrolylmagnesium halide and trichloroacetyl chloride.<sup>9</sup>

The present procedure provides a facile and versatile synthesis, on large scale, of a variety of pyrrole-2-carboxylic acid derivatives without necessitating the use of moisture-sensitive organometallic reagents. The use of alcohols other than ethanol in the alcoholysis reaction provides virtually any desired ester. Ammonia or aliphatic amines readily give amides in high yields, and aqueous base can be used to give the free acid.

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## HYDROGENATION OF AROMATIC NUCLEI: 1-DECALOL



Submitted by A. I. MEYERS,<sup>1</sup> W. N. BEVERUNG,<sup>2</sup> and R. GAULT<sup>3</sup>  
 Checked by P. FREIDENREICH and R. BRESLOW

### 1. Procedure

A 500 ml. Parr hydrogenation bottle is flushed with nitrogen and 20.0 g. of 5% rhodium-on-alumina (Note 1) is weighed directly into the hydrogenation bottle. The catalyst is wet by cautiously adding 25 ml. of 95% ethanol, and a solution of 40.0 g. (0.28 mole) of 1-naphthol (Note 2) in 125 ml. of 95% ethanol is added to the bottle with 3 ml. of acetic acid. The mixture is shaken in a Parr apparatus (Note 3) at an initial pressure of 55–60 p.s.i. of hydrogen. The theoretical hydrogen absorption is reached in about 12 hours (Note 4). The catalyst is then removed by suction filtration and washed twice with 50-ml. portions of ethanol (Note 5). The combined ethanol solutions are concentrated with a rotary evaporator to yield a viscous residue (39–41 g.). The residue is dissolved in 150 ml. of benzene, and the solution washed with 75 ml. of 10% sodium hydroxide solution and then with 75 ml. of water. The benzene solution is dried over magnesium sulfate for at least 3 hours and then concentrated with a rotary evaporator to give 39–41 g. (94–97%) of a mixture<sup>4</sup> consisting of the geometrical isomers of 1-decalol. *cis,cis*-1-Decalol may be isolated as a crystalline solid from the mixture by the addition of 15–20 ml. of heptane, followed by cooling. The product is isolated by filtration and recrystallized from a minimum amount of *n*-heptane to yield 13–14 g. (30–33%) of *cis,cis*-1-decalol, m.p.<sup>5</sup> 92–93°.

## 2. Notes

1. The catalyst is available from Engelhard Industries.

2. A purified grade of 1-naphthol should be used. Material available from Eastman Organic Chemicals, Aldrich Chemical Company, Inc., and Matheson Coleman and Bell is satisfactory. Experiments with technical grade 1-naphthol have indicated that this material requires purification by sublimation in order to give satisfactory results.

3. It has been found that the rhodium catalyst is not nearly as sensitive to poisoning as platinum or palladium catalyst. The metal inlet tube to the reaction bottle was merely rinsed with acetone, followed by ethanol, and the rubber stopper was soaked in 30–40% sodium hydroxide solution overnight.

4. A variety of experiments have shown that for bicyclic aromatic nuclei the weight ratio of reactant to catalyst should be 2:1, whereas for monocyclic aromatic nuclei, the reactant to catalyst ratio should be 3:1. For the latter systems, hydrogen absorption is usually complete within 6–8 hours (see Discussion section).

5. The catalyst may be reused after washing thoroughly with ethanol and drying at 125° for 12–15 hours. The activity, however, is somewhat decreased. *Care should be exercised never to leave the catalyst exposed to air in the presence of a flammable solvent.*

## 3. Discussion

1-Naphthol has been reduced to 1-decalol using platinum,<sup>5</sup> Raney nickel,<sup>6</sup> and Raney copper.<sup>7</sup> The reactions catalyzed by nickel and copper required elevated temperatures and pressure. The present procedure allows the preparation of substantial quantities of 1-decalol under much more convenient conditions and shorter reaction times. Previous methods<sup>5–7</sup> require costly catalysts or high-pressure equipment and frequently result in a high degree of hydrogenolysis. The submitters have found that the present method is applicable to a wide variety of aromatic nuclei, some of which are listed in Table I.

TABLE I  
HYDROGENATION OF AROMATIC NUCLEI<sup>a</sup>

Compound	g. Catalyst		Product	Yield, %
	g. Reactant			
2-Naphthol	0.50		2-Decalol <sup>b</sup>	88
2-Methylbenzofuran	0.33		<i>cis</i> -2-Methylhexahydro-benzofuran <sup>c</sup>	94
2,2-Dimethyl-2,3-dihydro-benzofuran	0.33		<i>cis</i> -2,2-Dimethylhexa-hydrobenzofuran <sup>c</sup>	91
3-Hydroxybenzoic acid	0.33		3-Hydroxycyclohexane-carboxylic acid <sup>b</sup>	81
4-Methoxyphenol	0.33		4-Methoxycyclohexanol <sup>b</sup>	88
Hydroquinone	0.33		1,4-Cyclohexanediol <sup>b</sup>	90
Resorcinol	0.33		1,3-Cyclohexanediol <sup>b</sup>	85

<sup>a</sup> From ref. 4.<sup>8</sup>

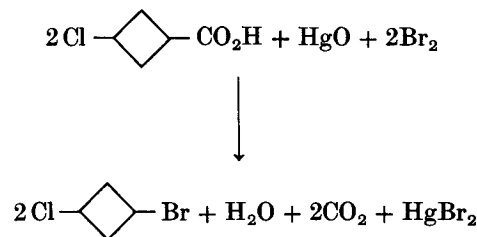
<sup>b</sup> Obtained as mixtures of geometric isomers.

<sup>c</sup> No detectable quantity of the *trans* isomer is obtained.

1. Department of Chemistry, Louisiana State University in New Orleans, New Orleans, Louisiana 70122. [Present address: Department of Chemistry, Wayne State University, Detroit, Michigan 48202.]
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1-bromo-3-chlorocyclobutane, b.p. 67–72° (45 mm.),  $n_D^{23}$  1.5065 (Notes 7 and 8).

**MERCURIC OXIDE-MODIFIED HUNSDIECKER REACTION:  
1-BROMO-3-CHLOROCYCLOBUTANE**



Submitted by GARY M. LAMPMAN and  
JAMES C. AUMILLER<sup>1</sup>  
Checked by G. NELSON and K. B. WIBERG

**1. Procedure**

In a 1-l. three-necked round-bottomed flask, wrapped with aluminum foil to exclude light, and equipped with a mechanical stirrer, a reflux condenser, and an addition funnel, is suspended 37 g. (0.17 mole) of red mercuric oxide (Note 1) in 330 ml. of carbon tetrachloride (Note 2). To the flask is added 30.0 g. (0.22 mole) of 3-chlorocyclobutanecarboxylic acid (Note 3), and the mixture is heated to reflux while stirring. To the mixture is added dropwise a solution of 40 g. (0.25 mole) of bromine in 180 ml. of carbon tetrachloride as fast as possible (4–7 minutes) without loss of bromine from the condenser (Note 4). After a short induction period, carbon dioxide is evolved at a rate of 150–200 bubbles per minute (Note 5). The solution is allowed to reflux until the rate of carbon dioxide evolution slows to about 5 bubbles per minute. This will usually take 25–30 minutes (Note 6). The mixture is then cooled in an ice bath, and the precipitate is removed by filtration. The residue on the funnel is washed with carbon tetrachloride, and the filtrates are combined. The solvent is removed by distillation using a modified Claisen distillation apparatus with a 6-cm. Vigreux column, and vacuum distillation of the residual oil gives 13–17 g. (35–46%) of

**2. Notes**

1. Purified product available from J. T. Baker Chemical Company.

2. Reagent-grade carbon tetrachloride was used.

3. G. M. Lampman and J. C. Aumiller, *Org. Syn.*, this volume, p. 73.

4. The heating bath should be maintained at about 120°. This is to ensure that the solution continues to reflux while the bromine solution is added.

5. The gas evolution can be monitored by conducting the gas through rubber tubing from the condenser into a small amount of water where the bubbling can be observed. A small amount of bromine is lost because of entrainment by the gas.

6. There is no increase in yield on heating the mixture under reflux for 3 hours.

7. The submitters reported a 48–52% yield (18–20 g.) using the indicated scale, and a 35% yield when the reaction was carried out using twice the scale. The checkers obtained the product in 28–29% yield when the reaction was conducted on a scale 10 times that indicated.

8. The product is analyzed by gas chromatography at 130° on a Beckman GC-2 chromatograph equipped with a 180 cm. × 6 mm. column (Beckman 17449) containing 42/60 Johns-Manville C-22 firebrick coated with Dow-Corning 550 silicone oil. The retention times are 12 and 14 minutes for the *trans* and *cis* compounds, respectively.

**3. Discussion**

This procedure, which is a modified Hunsdiecker reaction based upon the method of Cristol and Firth,<sup>2</sup> results in moderate to high yields of bromides and iodides from aliphatic<sup>2,3</sup> and alicyclic carboxylic acids.<sup>4–6</sup> Carbon tetrachloride is most frequently used as the solvent, but others can be employed.<sup>3,6</sup>

Attempts to prepare chlorides by the method have proved to be unsuccessful.<sup>7</sup>

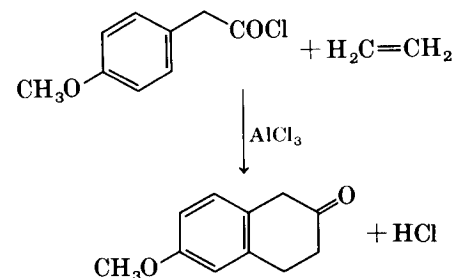
The main advantage of this procedure over that of the standard method<sup>8</sup> is one of convenience. For example, the present method is a one-step reaction while the usual method is a two-step sequence involving an intermediate silver salt. In addition, the presence of water produced in the reaction apparently does not reduce the yield in the present method while water markedly reduces the yield with the usual silver salt method.

Some variations of the method have been used to prepare cyclopropyl and cyclobutyl halides. Simultaneous addition of bromine and 3-bromocyclobutanecarboxylic acid to the suspension of mercuric oxide gives 1,3-dibromocyclobutane in good yield.<sup>7</sup> Similarly, cyclopropanecarboxylic acid gives bromocyclopropane,<sup>9</sup> and 3-(bromomethyl)cyclobutanecarboxylic acid gives 3-(bromomethyl)cyclobutyl bromide.<sup>10</sup> In the latter reaction, it was found desirable to remove the water from the reaction as it is formed in order to obtain high yields. Another variation is the addition of a mixture of the acid and mercuric oxide to excess bromine in bromotrichloromethane.<sup>6</sup>

The conversion of 1-bromo-3-chlorocyclobutane to bicyclo-[1.1.0]butane is described in *Organic Syntheses*.<sup>11</sup>

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**6-METHOXY- $\beta$ -TETRALONE**  
(2(1H)-Naphthalenone, 3,4-dihydro-6-methoxy-)



Submitted by JAMES J. SIMS, L. H. SELMAN and M. CADOGAN<sup>1</sup>  
Checked by ROBERT E. IRELAND and RONALD I. TRUST

### 1. Procedure

In a 2-l. three-necked flask equipped with a mechanical stirrer, a reflux condenser fitted with a calcium chloride drying tube, and a pressure-equalizing dropping funnel are placed 53.4 g. (0.4 mole) of anhydrous aluminum chloride (Note 1) and 800 ml. of dichloromethane (Note 2). The flask is placed in a dry ice-acetone bath, and the mixture is stirred for a few minutes before slowly adding a solution of 36.9 g. (0.2 mole) of *p*-methoxyphenylacetyl chloride (Note 3) in 200 ml. of dichloromethane over 45 minutes. When the addition is complete, the funnel is replaced by a gas inlet tube (Note 4), and ethylene is bubbled vigorously into the flask for about 10 minutes. The gas inlet tube is replaced with a stopper, the cooling bath is removed, and the reaction mixture is allowed to stir at room temperature for 3–3.5 hours (Note 5). The reaction mixture is cooled in an ice bath while 250 ml. of ice water is added *carefully* (Note 6). The mixture is stirred until all of the solid material is dissolved. The yellow organic layer is separated, washed two times with 150-ml. portions of 5% hydrochloric acid solution and two times with 150-ml. portions of saturated sodium bicarbonate solution. The organic layer is dried over magnesium

sulfate and the drying agent removed by filtration. The solvent is distilled on a rotary evaporator, keeping the bath temperature under 60°. Distillation (Note 7) of the yellow residue through a 15-cm. Vigreux column gives 21–24 g. (60–68%) of 6-methoxy- $\beta$ -tetralone, b.p. 114–116° (0.2 mm.). The product solidifies to a white solid on standing in the refrigerator, m.p. 33.5–35° (Note 8).

## 2. Notes

1. A 100% molar excess of aluminum chloride is necessary to obtain an acceptable yield in a short time. The reaction of phenylacetyl chloride with ethylene requires only 1 mole of aluminum chloride per mole of acid chloride.

2. Matheson Coleman and Bell dichloromethane, b.p. 39.5–40.5°, was used without purification. The use of this solvent rather than carbon disulfide is the major improvement of this procedure over the published one.<sup>2</sup>

3. *p*-Methoxyphenylacetyl chloride is prepared from *p*-methoxyphenylacetic acid (Aldrich Chemical Company, Inc., m.p. 85–86.5°) by the procedure of Buckles and Cooper<sup>3</sup> as follows. Thionyl chloride (50 ml.) is added to 100 g. (0.603 mole) of *p*-methoxyphenylacetic acid in a 500-ml. round-bottomed flask containing a few boiling stones and a magnetic stirring bar, and fitted with a calcium chloride drying tube. The contents of the flask are stirred slowly for 24 hours at room temperature. Dry benzene (80 ml.) is added and removed by distillation on a rotary evaporator twice. The yellow-green liquid is transferred to a 200-ml. flask with a little benzene and, after removal of the solvent under vacuum, distillation of the liquid through a 15-cm. Vigreux column affords 102–108 g. (92–97%) of *p*-methoxyphenylacetyl chloride, b.p. 80–88° (0.5 mm.).

4. A glass tube (6 mm. o.d.), flanged at one end and bent to direct gas bubbles in the direction of stirring is used. A fritted disk will become clogged during the addition and should not be used.

5. This reaction time was found to give the best yield of pure product. The progress of the reaction should be checked by

either infrared spectroscopy or vapor phase chromatography. A small aliquot (1–2 ml.) is worked up in a test tube by quenching with water, separating the organic phase, and drying over magnesium sulfate. The infrared spectrum will show a disappearance of the acid chloride carbonyl peak at 5.60  $\mu$  and appearance of the 6-methoxy- $\beta$ -tetralone carbonyl peak at 5.88  $\mu$ . Vapor phase chromatography is carried out in a 185 cm.  $\times$  3.2 mm. column packed with 5% by weight SE-30 on Diatoport S (60–80 mesh). The reaction may also be followed visually. The initial yellow suspension changes to green and finally to red-brown with a green cast. The reaction is essentially complete with the precipitation of dark green aluminum salts.

6. Much heat is generated on addition of water to the dark red-brown mixture. The addition should be dropwise until the heat is dissipated.

7. If the distillation is not carried out promptly, the crude product should be placed under nitrogen in a freezer. The tetralone seems to keep better under nitrogen at low temperature in glassware that has been rinsed with ammonium hydroxide and dried in an oven; the distillation flask and column were also routinely treated this way.

8. This material contains a small amount of impurity (2–5%). Purer material may be obtained by discarding a 1–2 g. fore-run.

## 3. Discussion

This procedure, which is an improvement over the method of Bueckhalter and Campbell,<sup>2</sup> represents the most convenient method of preparing 6-methoxy- $\beta$ -tetralone, a valuable intermediate for the synthesis of natural products. It also provides a general method for the synthesis of substituted  $\beta$ -tetralones.<sup>2,4</sup>

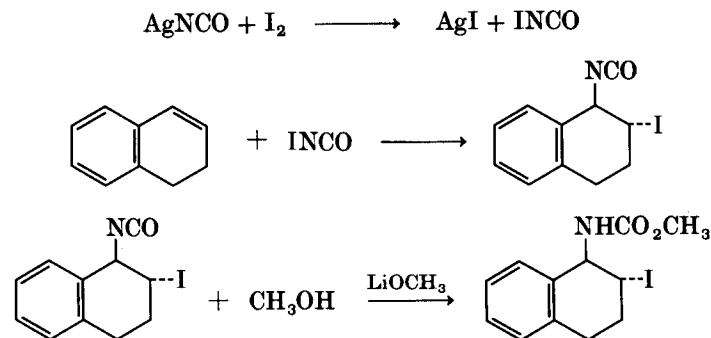
6-Methoxy- $\beta$ -tetralone has been synthesized from 6-methoxy-3,4-dihydronaphthalenecarboxylic acid by means of the Curtius reaction.<sup>5</sup> Other preparations include the Birch reduction of 6-methoxy-2-naphthol,<sup>6,7</sup> oxidation of 6-methoxytetralin,<sup>6,8</sup> and synthesis from 6-methoxy- $\alpha$ -tetralone.<sup>9</sup> The other practical approaches depend upon tedious preparations of naphthalene derivatives.



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### METHYL (*trans*-2-iodo-1-tetralin)carbamate

(1-Naphthalene carbamic acid, 1,2,3,4-tetrahydro-2-iodo-, methyl ester)



Submitted by C. H. HEATHCOCK<sup>1</sup> and A. HASSNER<sup>2</sup>  
 Checked by WILLIAM G. KENYON and RICHARD E. BENSON

#### 1. Procedure

A 1-l. three-necked round-bottomed flask fitted with a mechanical stirrer, a thermometer, and a calcium chloride drying tube is immersed in an ice-salt bath. To the flask are added 38 g. (0.25 mole) of silver cyanate (Note 1), 34.7 g. of 75% 1,2-

dihydronaphthalene (0.20 mole, Note 2), and 400 ml. of anhydrous ether. Stirring is begun and when the temperature of the contents of the flask has reached 0°, 50.8 g. (0.20 mole) of iodine is added in one portion. The brown mixture is stirred vigorously for 2 hours at 0–5° and then for 6 hours at room temperature. The resulting mixture, which still retains the color of iodine, is filtered through a layer of filter aid. The filtrate is transferred to a 1-l. separatory funnel and is washed with 75-ml. portions of 15% sodium bisulfite solution until the ether layer is nearly colorless. The resulting ether solution is concentrated to 200 ml. using a rotary evaporator at room temperature and 20 mm. pressure.

A solution of lithium methoxide, prepared from 0.015 g. of lithium in 200 ml. of methanol, is added to the ether solution, and the resulting mixture is allowed to stand at room temperature for 1 hour. The volume is reduced to 200 ml. by distillation using a rotary evaporator at room temperature and 20 mm. pressure, and the solution is added to 600 ml. of an ice-water mixture containing 3 g. of sodium bisulfite. The solid product that separates is collected by filtration, washed with water, and dried in air. The crude carbamate, which weighs 57–64 g., is dissolved in 180 ml. of hot methanol. The resulting mixture, which is slightly cloudy, is filtered rapidly through a coarse fluted filter paper. The filtrate is warmed to redissolve the product, and 30 ml. of water is added slowly while the solution is heated. The flask is allowed to stand overnight and then is cooled to 0° to yield a crystalline solid which is collected by filtration. The product is washed with 10 ml. of ice-cold methanol-water mixture (4:1) and is dried in air. The yield of methyl (*trans*-2-iodo-1-tetralin)carbamate, m.p. 125.5–126.5°, is 39.6–41.0 g. (60–62%). The infrared spectrum (KBr wafer) shows strong absorption at 3220 and 1685 cm.<sup>-1</sup>.

#### 2. Notes

1. The purity of the silver cyanate used seems to be critical. Best results are obtained using product prepared in the following manner. A solution of 100 g. (0.59 mole) of silver nitrate in

3 l. of distilled water is added to a solution of 49.5 g. (0.61 mole) of potassium cyanate in 700 ml. of distilled water. The white precipitate is recovered by filtration and washed successively with distilled water, methanol, and ether. The product is protected from light and air-dried overnight on a filter funnel attached to an aspirator. The product is then dried over phosphorous pentoxide under vacuum for at least 24 hours.

2. The submitters used technical grade dihydronaphthalene of 83% purity (Columbia Organic Chemicals Company, Inc.) or of 75% purity (Aldrich Chemical Company, Inc.) as indicated by gas chromatography. The checkers used the Aldrich product.

### 3. Discussion

The addition of iodine isocyanate to olefins is a general reaction leading stereospecifically to *trans*- $\beta$ -iodoisocyanates convertible to *trans*- $\beta$ -iodocarbamates or ureas.<sup>3</sup> The procedure described here is essentially that of Hassner and Heathcock.<sup>3</sup> The method is applicable to unsaturated alcohols, esters, ketones, and dienes but not to conjugated unsaturated esters or ketones. The effect of solvent on the rate of reaction for the addition of iodine isocyanate to cyclohexene has been studied.<sup>4</sup> The rate of reaction in methylene chloride was found to be much greater than that in ether. Stereochemical and regiochemical effects as well as possible rearrangements during the addition have been evaluated.<sup>5</sup>  $\beta$ -Iodocarbamates serve as useful intermediates in the synthesis of aziridines,<sup>3,6,7</sup> azepines,<sup>8</sup> 1,2-diamines,<sup>9</sup> carbamates,<sup>5</sup> oxazolidones,<sup>10</sup> and amino alcohols.<sup>10</sup>

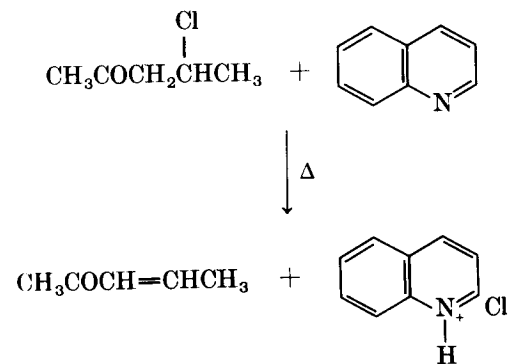
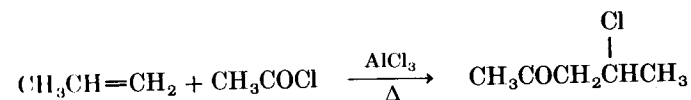
The conversion of methyl (*trans*-2-iodo-1-tetralin)carbamate to 1,2,3,4-tetrahydronaphthalene(1,2)imine is described in *Organic Syntheses*.<sup>7</sup>

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### *trans*-3-PENTEN-2-ONE

(*trans*-3-Penten-2-one)



Submitted by H. C. ODOM and A. R. PINDER<sup>1</sup>  
 (Checked by WALTER J. CAMPBELL and HERBERT O. HOUSE)

### 1. Procedure

*Caution:* Since both hydrogen chloride and propylene may escape from the reaction vessel during this preparation, the reaction should be performed in a hood.

A 2 l. three-necked flask is equipped with an efficient mechanical stirrer, a gas inlet tube extending almost to the bottom of the flask, and an efficient reflux condenser fitted with a calcium chloride filled drying tube. After the apparatus has been dried in

an oven, 800 ml. of methylene chloride (Note 1) and 157 g. (142 ml., 2.0 moles) of acetyl chloride (Note 2) are added to the flask. This solution is stirred while 320 g. (2.4 moles) of powdered anhydrous aluminum chloride (Note 3) is added in portions over a 15-minute period. As soon as this addition is complete, a stream of propylene gas (Note 4) is passed through the continuously stirred reaction solution at a sufficient rate to maintain a gentle reflux. The gas flow is continued until no more heat is evolved and refluxing ceases (10–30 hours, Note 4) at which time the flask is nearly full and the contents separate into two layers when stirring is stopped. The contents of the flask are poured cautiously onto about 1.5 kg. of ice (Note 5), and the upper organic layer is separated. The aqueous phase is shaken with three 100-ml. portions of methylene chloride (Note 6) and the combined organic solutions are washed with 50 ml. of water and dried over anhydrous magnesium sulfate.

The resulting dark brown solution is placed in a 2-l. round-bottomed flask equipped with a thermometer, a magnetic stirring bar, a heating mantle, and a suitable assembly of a distilling head, a condenser, and a receiver to permit distillation under reduced pressure. The bulk of the methylene chloride and volatile hydrocarbons are distilled from the mixture at water-aspirator pressure while sufficient heat is supplied with the heating mantle to maintain the temperature of the mixture at about 0° (Note 7). When the bulk of the solvent has been removed, a 1-l. round-bottomed flask, cooled in a dry ice-isopropyl alcohol bath, is attached to the apparatus as a receiver, and the pressure is reduced to 1 mm. or less with a vacuum pump. Heat is supplied with the heating mantle so that the temperature of the viscous liquid in the distillation flask slowly rises from about 0° to 45° over a period of 90 minutes while the volatile products (methylene chloride, low molecular-weight hydrocarbons, 4-chloropentan-2-one, and 3-penten-2-one) distil (Note 7). The resulting distillate (400–500 g. of pale green liquid) is mixed with 256 g. (1.98 moles) of quinoline (Note 8) and then heated to boiling. In order to remove the remaining methylene chloride and other low-boiling materials (Note 9), liquid is allowed to distil from the mixture until the

temperature of the distilling liquid reaches 110–120°. The remaining solution is refluxed for 30 minutes and then cooled and diluted with the previously removed distillate and 200 ml. of pentane. The resulting solution is washed with successive 250-ml. portions of aqueous 10% hydrochloric acid until the aqueous washings are acidic. The aqueous washings are combined, acidified, and shaken with three 100-ml. portions of pentane. The combined organic solutions are washed with 50 ml. of saturated aqueous sodium bicarbonate and then dried over anhydrous magnesium sulfate. The resulting organic solution is fractionally distilled through a 30-cm. Vigreux column, and the product is collected in the fraction boiling at 119–124°. This crude product amounts to 42–63 g. (25–37%) and contains 3-penten-2-one of 86–92% purity (Note 10). If a product of greater purity is desired, the product may be distilled through a 60-cm. spinning band column. Since this distillation may be accompanied by partial isomerization of the  $\alpha,\beta$ -unsaturated ketone to the lower boiling  $\beta,\gamma$ -isomer (Note 10), the product from the fractional distillation should be subjected to an acid-catalyzed equilibration. In a typical purification 79.4 g. of a mixture of penten-2-one isomers, b.p. 117–119°, from a fractional distillation is mixed with 400 mg. of *p*-toluenesulfonic acid and refluxed for 30 minutes. The resulting mixture is diluted with 100 ml. of ether and then washed with 50 ml. of saturated aqueous sodium bicarbonate and dried over anhydrous magnesium sulfate. The resulting ether solution is fractionally distilled through a 16-cm. Vigreux column to give 60.4 g. of *trans*-3-penten-2-one of 97% purity, b.p. 121.5–124°,  $n_D^{25}$  1.4329 (Note 11).

## 2. Notes

1. The methylene chloride was dried over calcium chloride before use.

2. The submitters used a practical grade of acetyl chloride obtained from Eastman Organic Chemicals. The checkers used reagent-grade acetyl chloride obtained from the Industrial Chemicals Division, Allied Chemical Corporation.

3. The reagent grade of powdered, anhydrous aluminum chloride employed was obtained from the Specialty Chemicals Division, Allied Chemical Corporation.

4. A chemically pure grade of propylene obtained from Matheson Gas Products was employed. A large excess of propylene is used in this preparation since much of the olefin is converted to polymeric products. The submitters report obtaining markedly lower yields of product when an excess of propylene was not used.

5. At this point there should be only a relatively mild exothermic reaction as the anhydrous aluminum salts are hydrolyzed and solvated.

6. In these extractions the organic layer is the lower one.

7. The submitters had originally distilled the volatile products from this mixture, containing mainly polymeric material, by a more conventional procedure. However, the checkers found the problems from foaming during the distillation so severe that the alternative low-temperature distillation procedure was adopted.

8. The practical grade of quinoline employed was obtained from Aldrich Chemical Company, Inc.

9. The reaction solution must reach a temperature of approximately 90° for rapid dehydrochlorination to occur. If low-boiling impurities prevent the reaction mixture from reaching this temperature, the final product may be contaminated with the intermediate  $\beta$ -chloroketone. On a gas chromatography column packed with Carbowax 20M suspended on Chromosorb P, the retention times for the  $\alpha,\beta$ -unsaturated ketone and the intermediate  $\beta$ -chloroketone are 4.9 minutes and 12.0 minutes, respectively. A sample of 4-chloro-2-pentanone, collected from this gas chromatography column, has infrared absorption (chloroform solution) at 1720  $\text{cm}^{-1}$  ( $\text{C}=\text{O}$ ) with n.m.r. absorption (deuteriochloroform solution) at 4.45 (sextuplet,  $J = 7$  Hz., 1H,  $\text{CHCl}$ ), 2.5–3.3 (multiplet, 2H,  $\alpha\text{-CH}_2$ ), 2.20 (singlet, 3H,  $\text{CH}_3\text{CO}$ ), and 1.55 p.p.m. (doublet,  $J = 7$  Hz., 3H,  $\text{CH}_3$ ).

10. The product was analyzed with a 2-m. gas chromatography column packed with Carbowax 20M suspended on

Chromosorb P. In chromatograms obtained from this column at 100°, the retention times of 4-penten-2-one and 3-penten-2-one are 2.6 and 3.9 minutes, respectively. The crude product contains several additional low-boiling components with gas chromatographic retention times in the range 1.6–2.8 minutes. Any 4-penten-2-one present as an impurity exhibits infrared absorption (carbon tetrachloride solution) at 1720  $\text{cm}^{-1}$  (nonconjugated  $\text{C}=\text{O}$ ).

11. The pure *trans*-3-penten-2-one has infrared absorption (carbon tetrachloride solution) at 1680 and 1705  $\text{cm}^{-1}$  (cisoid and transoid conformers<sup>2</sup> of the conjugated  $\text{C}=\text{O}$ ), 1635  $\text{cm}^{-1}$  (conjugated  $\text{C}=\text{C}$ ), and 970  $\text{cm}^{-1}$  (*trans*- $\text{CH}=\text{CH}$ ) with an ultraviolet maximum (95% EtOH solution) at 220  $\text{m}\mu$  ( $\epsilon$  11,000) and n.m.r. absorption (deuteriochloroform solution) at 6.85 (doublet of quadruplets,  $J = 7$  and 16 Hz., 1H,  $\beta$ -vinyl CH), 6.10 (doublet of partially resolved multiplets,  $J = 16$  Hz., 1H,  $\alpha$ -vinyl CH), 2.22 (singlet, 3H,  $\text{CH}_3\text{CO}$ ), and 1.88 p.p.m. (doublet of doublets,  $J = 1.5$  and 7 Hz., 3H,  $\text{CH}_3$ ). The mass spectrum of the product has the following relatively abundant peaks:  $m/e$  (relative intensity), 84( $\text{M}^+$ , 36), 69(100), 43(57), 41(78), and 39(33).

### 3. Discussion

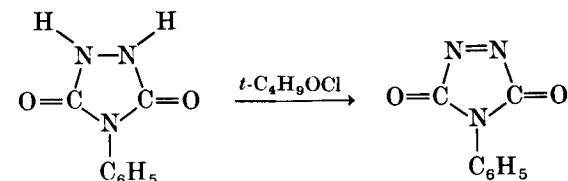
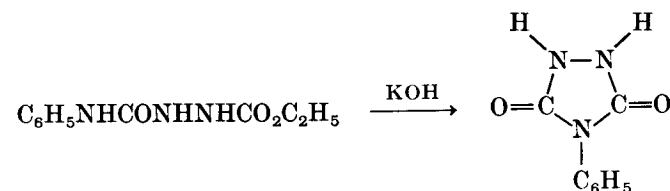
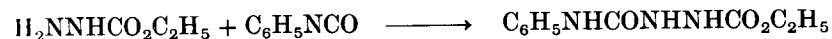
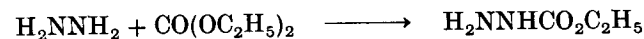
*trans*-3-Penten-2-one has been prepared by the dehydration of 4-hydroxy-2-pentanone with heat,<sup>3</sup> acetic anhydride,<sup>3</sup> sulfuric acid,<sup>4</sup> or iodine.<sup>5</sup> It has also been obtained by fractional distillation of a commercial product resulting from an aldol condensation of acetaldehyde and acetone.<sup>6</sup> Preparations are described involving reaction between acetyl bromide and propylene, in the presence of anhydrous aluminum bromide,<sup>7</sup> and between acetic anhydride or acetyl chloride and propylene in the presence of anhydrous aluminum chloride.<sup>8</sup> Other preparative methods include the oxidation of *trans*-3-penten-2-ol with chromic acid<sup>6</sup> and the Wittig reaction between acetyl-methylenetriphenylphosphorane and acetaldehyde.<sup>9</sup>

The present procedure, an adaption of one described previously,<sup>8</sup> illustrates the acylation of an olefin in the presence of

a Lewis-acid catalyst. Although this method may lead to complex mixtures of acylated products when higher molecular-weight olefins are acylated in the presence of excess aluminum chloride, the application of this procedure to propylene gives a single monomeric acetylated product accompanied by a complex mixture of low molecular-weight hydrocarbons and unidentified, higher molecular-weight materials. The relatively low boiling point of the monoacetylated product permits its ready separation from most of the components of this mixture after which it is dehydrochlorinated to form the desired product. The product of this reaction is obtained in sufficient purity to serve as a synthetic intermediate in annelation reactions with cycloalkanones.<sup>10</sup>

#### 4-PHENYL-1,2,4-TRIAZOLINE-3,5-DIONE

( $\Delta^1$ -1,2,4-Triazoline-3,5-dione, 4-phenyl-)



Submitted by R. C. COOKSON, S. S. GUPTA,  
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Checked by Y. CHAO and R. BRESLOW

#### 1. Procedure

**A. Ethyl hydrazinecarboxylate.** To 100 g. (97 ml., 2.0 moles) of 100% hydrazine hydrate, contained in a 1-l. round-bottomed flask, is added 236 g. (243 ml., 2.0 moles) of diethyl carbonate (Note 1). The flask is fitted with a calcium chloride-containing drying tube and is shaken vigorously to mix the two liquids. After about 5 minutes, the milky emulsion becomes warm, and shaking is continued until a clear solution is obtained (approximately 20 minutes). The flask is equipped with a reflux condenser fitted with a calcium chloride-containing drying tube and is heated on a steam bath for 3.5 hours. The reaction mixture is transferred to a 500-ml. round-bottomed flask and is

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distilled through a 15-cm. Vigreux column under reduced pressure. The product is collected as a colorless liquid boiling at 102–103° (18 mm.) or 117–118° (40 mm.) (Note 2). The yield is 161–176 g. (77–85%),  $n_{D}^{25}$  1.4495,  $\nu_{\max}$  1640, 1725, and 3350  $\text{cm}^{-1}$ . The product may crystallize on standing, m.p. 45–47°. No further purification is needed before using this material for the next step.

B. *4-Phenyl-1-carbethoxysemicarbazide*. In a 1-l. three-necked round-bottomed flask equipped with a liquid-sealed mechanical stirrer (Note 3), a constant-pressure dropping funnel, and a reflux condenser fitted with a drying tube containing silica gel is placed a solution of 52 g. (0.5 mole) of ethyl hydrazine-carboxylate in 550 ml. of dry benzene (Note 4). The solution is cooled in an ice bath, and the stirrer is started. To the solution is added 59.7 g. (55 ml., 0.5 mole) of phenyl isocyanate (Note 5) dropwise over a period of 45 minutes. After about one-half of the isocyanate has been added, a white precipitate of the product appears, and the reaction mixture becomes progressively thicker. After addition is complete the ice bath is removed, and the mixture is stirred at room temperature for 2 hours and then is heated under reflux for 2 hours. The suspension is allowed to cool to room temperature, and 4-phenyl-1-carbethoxysemicarbazide is isolated by suction filtration, washed with 500 ml. of benzene, and dried in a vacuum desiccator. The yield is 108 g. (97%), m.p. 151–152°. The product is not further purified before being used in the next step. It may be recrystallized from ethyl acetate to yield white crystals, m.p. 154–155°,  $\nu_{\max}$  1645, 1687, 1797, and 3300  $\text{cm}^{-1}$  (Note 6).

C. *4-Phenylurazole*. In a 250-ml. Erlenmeyer flask are placed 100 ml. of 4*M* aqueous potassium hydroxide and 44.6 g. (0.2 mole) of 4-phenyl-1-carbethoxysemicarbazide. The suspension is warmed on a steam bath, the flask being swirled occasionally to wash the solid off the sides. After 1.5 hours most of the solid has dissolved, and the hot solution is filtered. After cooling to room temperature, the solution is acidified with concentrated hydrochloric acid (about 33 ml. is required). The mixture is again cooled to room temperature and the precipitated 4-phenylurazole is isolated by suction filtration. The mother liquor

is evaporated to dryness on a rotary evaporator, and the residue is extracted two times with 100-ml. portions of boiling absolute ethanol (Note 7). The ethanol solutions are combined, filtered, and evaporated to dryness on a rotary evaporator, and the additional 4-phenylurazole recovered is combined with that obtained above. The product is crystallized from 95% ethanol (about 80 ml.) to yield 30.0–33.5 g. (85–95%) of 4-phenylurazole, m.p. 209–210°  $\nu_{\max}$  1685 and 3120  $\text{cm}^{-1}$ . (Notes, 8, 9, and 10).

D. *4-Phenyl-1,2,4-triazoline-3,5-dione*. A 100-ml. three-necked round-bottomed flask, equipped with a dropping funnel, a gas inlet tube, a calcium chloride-containing drying tube, and a magnetic stirrer, is flushed with oxygen-free nitrogen (Note 11). To the flask are added 12 ml. of ethyl acetate (Note 12) and 4.4 g. (0.025 mole) of 4-phenylurazole (Note 13), and the stirrer is started. To the flask is added 2.5 g. (2.75 ml., 0.023 mole) of *t*-butyl hypochlorite (Notes 14 and 15) over a period of approximately 20 minutes, the reaction mixture being maintained close to room temperature by means of a bath of cold water (Notes 16 and 17). After the addition is complete, the resulting suspension is stirred for a further 40 minutes at room temperature. The reaction mixture is transferred to a 100-ml. one-necked round-bottomed flask, and the solvent is removed on a rotary evaporator, keeping the temperature below 40°. The last traces of solvent are removed by use of a high-vacuum pump (about 0.1 mm.). The product is sublimed (Note 18) onto an ice-cooled cold finger under vacuum (100° at 0.1 mm.). Carmine-red crystals, which decompose (165–175°) before melting, are obtained. The yield is 2.7–2.8 g. (62–64%);  $\nu_{\max}$  1760 and 1780  $\text{cm}^{-1}$ ;  $\lambda_{\max}$  (dioxane) 247 ( $\epsilon$  2300), 310 (1020), and 532 nm. (171) (Notes 19 and 20).

## 2. Notes

1. Both the hydrazine hydrate and diethyl carbonate were British Drug Houses Ltd. or Matheson Laboratory reagent grade and were used without further purification.

2. A fore-run of approximately 100 ml., boiling below 80° (18 mm.), is also collected. This contains ethanol, water, and unreacted starting materials.

3. An efficient stirrer should be employed, since the reaction mixture becomes quite viscous, and if efficient mixing is not maintained a violent reaction can occur. This is especially important when using aliphatic isocyanates.

4. British Drug Houses Ltd. or Amend Drug & Chemical Co., Inc. reagent-grade benzene, dried over sodium wire, is adequate.

5. British Drug Houses Ltd. or Matheson Laboratory reagent-grade phenyl isocyanate was used without further purification. When using other isocyanates, care should be taken to ensure their purity as the yield is greatly dependent upon this, commercially available *p*-nitrophenyl isocyanate being a case in point.

6. The submitters report a similar yield on a scale three times that illustrated here. This method has been employed for the preparation of the 4-methyl- (100%, m.p. 143° from ethyl acetate), 4-*t*-butyl- (100%, m.p. 147° from ethyl acetate), and 4-*p*-nitrophenyl-1-carbethoxysemicarbazide (90%, m.p. 219° from methanol). Because of the impure nature of commercial *p*-nitrophenyl isocyanate, the product from that reaction may be contaminated with *p*-nitrophenylurea. It can be used in this impure form for preparing the corresponding urazole, as the contaminant is alkali insoluble.

7. The extraction procedure increases the yield of 4-phenylurazole by about 6%. This step is unnecessary when preparing 4-*p*-nitrophenylurazole, as it is insoluble in water.

8. This method has been used to prepare 4-methyl- (90%, m.p. 240° from methanol) and 4-*p*-nitrophenylurazole (80%, m.p. 264° from ethanol).

9. 4-*t*-Butyl-1-carbethoxysemicarbazide can be cyclized by refluxing with 4% sodium ethoxide in ethanol for 4 hours, followed by acidification with an ethanolic solution of hydrogen chloride. Filtration, evaporation of the filtrate, and crystallization from ethyl acetate yields 4-*t*-butylurazole (89%, m.p. 168°).

10. 4-Benzalaminourazole (m.p. 255°) can be prepared from 4-aminourazole<sup>2</sup> by condensation with benzaldehyde.

11. A gentle stream of nitrogen is maintained through the apparatus during the entire reaction. Hydrogen chloride is

evolved and adequate precautions should be taken to prevent exposure to the gas.

12. The ethyl acetate was purified by Fieser's method.<sup>3</sup>

13. The 4-phenylurazole should be ground with a pestle and mortar before use.

14. *t*-Butyl hypochlorite was prepared by the method described in *Organic Syntheses*.<sup>4</sup>

15. An excess of *t*-butyl hypochlorite should not be used, as it cannot be removed and it interferes with the sublimation of the product.

16. When preparing the 4-*p*-nitrophenyl and 4-benzalamino analogs, the reaction mixture should be maintained at 0–5°.

17. As soon as the first drop of hypochlorite is added, the reaction mixture becomes red in color, the color deepening as the addition proceeds.

18. The impure material has a limited stability and should be sublimed as quickly as possible. The scale of the reaction should not be greatly increased unless an efficient large subliming apparatus is available. The submitters report similar yields on experiments four times this scale.

19. The product has a shelf life of several months if stored in the dark in a refrigerator.

20. This method has been used to prepare 4-methyl- [sublimed at 50° (0.1 mm.), 85%, m.p. 104°], 4-*t*-butyl- [50° (0.1 mm.), 80%, m.p. 119°], 4-*p*-nitrophenyl- [100° (0.1 mm.), 25%, m.p. 130°], and 4-benzalamino-1,2,4-triazoline-3,5-dione [100° (0.1 mm.), 75%].

### 3. Discussion

Ethyl hydrazinecarboxylate has been prepared from hydrazine hydrate and ethyl N-tricarboxylate in good yield.<sup>5</sup> The method described here is comparable in efficiency but has the added advantage that both starting materials are commercially available.

The methods for preparing 4-phenyl-1-carbethoxysemicarbazide and 4-phenylurazole have been described in principle by Zinner and Deucker.<sup>6</sup> 4-Phenylurazole has also been prepared from biurea and aniline hydrochloride;<sup>7,8</sup> the method,

however, is unreliable, with yields varying from 0 to 20%. 4-Substituted urazoles have also been made by heating the corresponding N,N'-disubstituted diamides of hydrazodicarboxylic acid,<sup>9</sup> but the results are difficult to reproduce.

4-Phenyl-1,2,4-triazoline-3,5-dione has been prepared by oxidizing 4-phenylurazole with lead dioxide,<sup>7</sup> and with ammoniacal silver nitrate followed by an ethereal solution of iodine.<sup>8</sup> The yields are low for both methods. 4-Substituted triazoline-diones can also be made by oxidation of the corresponding urazole with fuming nitric acid<sup>9</sup> or dinitrogen tetroxide.<sup>10</sup> Oxidation by *t*-butyl hypochlorite in acetone solution has also been described;<sup>11,12</sup> it, however, yields an unstable product, even after sublimation. Either dioxane<sup>12</sup> or ethyl acetate are preferred as solvents for the reaction, since the product is obtained in a stable form. The latter solvent is superior since 4-phenylurazole has a greater solubility in it.

In common with other azodicarboxylic acid derivatives, the uses of 4-phenyl-1,2,4-triazoline-3,5-dione are many. It undergoes a Diels-Alder reaction with most dienes<sup>11-14</sup> and is, in fact, the most reactive dienophile so far reported.<sup>15,16</sup> As with the formation of all Diels-Alder adducts the reaction is reversible, and in the case of the adduct with 3- $\beta$ -acetoxy-17-cyano-5,14,16-androstatriene, the reverse reaction can be made to proceed under especially mild conditions.<sup>14</sup> An instance has also been reported of the dione photochemically catalyzing other retro Diels-Alder reactions.<sup>17</sup> Along with the proven use of azodicarboxylic ester,<sup>18,19</sup> the dione should be potentially important in the preparation of strained ring compounds.

4-Phenyl-1,2,4-triazoline-3,5-dione also undergoes "addition-abstraction" reactions (e.g., with acetone<sup>17</sup>). As would be expected for such a species, it will oxidize alcohols to the corresponding aldehydes or ketones.<sup>20</sup> This oxidation is especially mild (room temperature in benzene, chlorobenzene or ethyl acetate) and so is a valuable method of oxidizing, or preparing, compounds sensitive to acid, base, or heat.

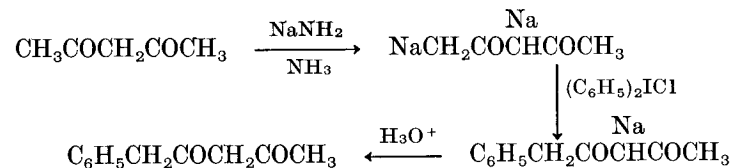
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**PHENYLATION WITH DIPHENYLIODONIUM CHLORIDE:  
1-PHENYL-2,4-PENTANEDIONE**



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Checked by WILLIAM N. WASHBURN and RONALD BRESLOW

### 1. Procedure

*Caution: This preparation should be carried out in an efficient hood to avoid exposure to ammonia.*

A 1-l. three-necked flask is equipped with an air condenser (Note 1), a ball-sealed mechanical stirrer, and a glass stopper. The stopper is removed, and 800 ml. of anhydrous liquid ammonia is introduced from a cylinder through an inlet tube. The tube is removed and replaced by the stopper. To the stirred ammonia is added a small piece of sodium. After the appearance of a blue color a few crystals of ferric nitrate hydrate (about 0.25 g.) are added, followed by small pieces of freshly cut sodium until 18.4 g. (0.80 g. atom) has been added. After the formation of sodium amide is complete (Note 2), the glass stopper is replaced by a pressure-equalizing dropping funnel containing 40.0 g. (0.400 mole) of 2,4-pentanedione (Note 3) in 30 ml. of anhydrous ether. The top of the addition funnel is fitted with a nitrogen inlet tube. The reaction flask is immersed at least 3 inches into a dry ice-acetone bath (Note 4), and simultaneously the slow introduction of dry nitrogen through the inlet tube is begun. After the reaction mixture is cooled thoroughly (about 20 minutes), the solution of 2,4-pentanedione is added intermittently in small portions (Note 4) over 10 minutes. The cooling bath is then removed, and the nitrogen flow is stopped. After 30 minutes the addition funnel is removed and 63.3 g.

(0.200 mole) of diphenyliodonium chloride (Note 5) is added through Gooch tubing from an Erlenmeyer flask over 15–25 minutes (Note 6). The reaction mixture is stirred for 6 hours, during which time gradual evaporation of ammonia occurs. The Gooch tubing is replaced by an addition funnel and 400 ml. of anhydrous ether is added. The remaining ammonia is removed by cautious heating on a warm-water bath. After the ether has distilled gently for 15 minutes, the flask is cooled in an ice-water bath, and 200 g. of crushed ice is added. A mixture of 60 ml. of concentrated hydrochloric acid and 10 g. of crushed ice is then added. The reaction mixture is stirred until the solid material has dissolved (Note 7) and then is transferred to a separatory funnel, the flask being washed with a little ether and dilute hydrochloric acid. The ethereal layer is separated, and the aqueous layer (Notes 8 and 9) is shaken three times with 50-ml. portions of ether. The combined ethereal extracts are dried over anhydrous magnesium sulfate. After filtration and removal of the solvent, the residual oil is purified by vacuum distillation to give 21.0–22.5 g. (60–64%) (Note 10) of 1-phenyl-2,4-pentanedione, b.p. 133–136° (10 mm.), as a colorless to light yellow liquid (Note 11).

### 2. Notes

1. The flask is insulated by wrapping with cloth towels in order to reduce the rate of ammonia evaporation. In addition the towels exclude light thus reducing the photolytic production of iodine from diphenyliodonium chloride and the reaction products.

2. Conversion to sodium amide is indicated by the disappearance of the blue color. This generally requires about 20 minutes.

3. 2,4-Pentanedione, obtained from Aldrich Chemical Company, Inc., was dried over potassium carbonate and distilled before use, the fraction b.p. 133–135° being used.

4. The addition of 2,4-pentanedione to liquid ammonia is a highly exothermic process. Also, ammonia vapor reacts with the  $\beta$  diketone to produce an insoluble ammonium salt, which tends to clog the tip of the addition funnel. Cooling the reaction

mixture in a dry ice-acetone bath reduces the vigor of the reaction and minimizes the clogging of the addition funnel. The 2,4-pentanedione should be added in spurts which fall on the surface of the reaction mixture rather than on the wall of the flask.

5. Diphenyliodonium chloride prepared by the method of Beringer and co-workers was used.<sup>4</sup> The diphenyliodonium chloride can also be prepared by the method described in *Organic Syntheses*,<sup>5</sup> or may be purchased from Aldrich Chemical Company, Inc.

6. If the addition is too fast, the reaction mixture will foam out of the flask.

7. A little diphenyliodonium salt may remain which will not dissolve. It will settle between the layers.

8. The aqueous layer should be acidic to litmus paper. If it is basic, more hydrochloric acid should be added until an acidic test is obtained.

9. The ethereal solution is usually dark but should not have a purple color. A purple color indicates the presence of iodine. Iodine can arise by light-catalyzed reaction in the latter stages of the reaction and during isolation of the product. For this reason the reaction should be shielded from strong light. In addition it is advisable for the ether employed in the reaction mixture to be peroxide-free. If iodine is present in the reaction product, it must be removed by extraction with aqueous sodium thiosulfate solution since an adequate separation is not obtained by distillation.

10. The submitters have obtained the product in yields as high as 92% by a similar procedure and 85–91% by this procedure on this scale. The yield is calculated with the assumption that only one of the phenyl groups of diphenyliodonium ion is available for phenylation. This is not rigorously true; however, the magnitude of error is not great.<sup>6</sup>

11. A fore-run of 2,4-pentanedione and iodobenzene, b.p. 32–92° (35 mm.), is obtained and then the pressure is reduced to 10 mm. The purity of the product may be demonstrated by gas chromatography at 130° using a 180-cm. column packed with silicone gum rubber (Hewlett-Packard Co.). The chromatogram

obtained showed only traces of iodobenzene and 3-phenyl-2,4-pentanedione.

### 3. Discussion

The method described is that of Hampton, Harris, and Hauser<sup>6</sup> and is an improvement over the benzyne method, which gives poor yields.<sup>6,7</sup> This  $\beta$ -diketone has been prepared by Claisen condensation of ethyl phenylacetate with acetone,<sup>8</sup> but the yield is poorer and the product has been shown by gas chromatography to be impure.<sup>6</sup> The  $\beta$ -diketone has also been prepared by the hydrolysis of 4-methoxy-5-phenyl-3-penten-2-one<sup>9</sup> and by hydrolysis and decarboxylation of ethyl  $\alpha$ -acetyl- $\beta$ -oxo- $\gamma$ -phenylbutyrate<sup>10</sup> but these compounds are more difficult to obtain than the starting materials used in the present synthesis.

This procedure represents a novel, convenient, and fairly general method for preparing  $\gamma$ -aryl- $\beta$ -diketones. By this method the submitters have phenylated the dianion of 1-phenyl-1,3-butanedione (61%), 2,4-heptanedione (98%), 2,4-nonanedione (78%), 2,4-tridecanedione (53%), and 3,5-heptanedione (50%).<sup>6</sup> Substituted diaryliodonium salts have also been used to produce 1-(4-chlorophenyl)-2,4-pentadione (44%), 4-(4-methylphenyl)-1-phenyl-1,3-butanedione (44%), and 1-(4-methylphenyl)-2,4-nonanedione (21%).<sup>6</sup> Under these conditions no more than a trace, if any, of arylation at the  $\alpha$ -position of the  $\beta$ -diketones was observed by gas chromatography analysis.

Although the phenylation of monoanions of  $\beta$ -diketones does not proceed at a significant rate under the present conditions, phenylation of monoanions using diphenyliodonium salts under somewhat more vigorous conditions has been observed. The monoanions of 5,5-dimethyl-1,3-cyclohexanedione,<sup>11,12</sup> dibenzoylmethane,<sup>11</sup> tribenzoylmethane,<sup>11</sup> 1,3-indandione,<sup>13</sup> 2-mesityl-1,3-indandione,<sup>14</sup> and 2-phenyl-1,3-indandione<sup>13</sup> have been phenylated to give the mono- or diphenylated products. Ketoesters such as ethyl 1,3-indandione-2-carboxylate,<sup>13</sup> ethyl cyclohexanone-2-carboxylate,<sup>15</sup> and other esters such as ethyl phenylacetate,<sup>15</sup> ethyl diphenylacetate,<sup>15</sup> diethyl acetamidomalonnate,<sup>15</sup> diethyl ethylmalonnate,<sup>15</sup> diethyl phenylmalonnate,<sup>15</sup>

and diethyl malonate<sup>16</sup> have been arylated in fair to good yields. Kornblum and Taylor have also found that nitroalkanes can be phenylated in 54–69% yield. These include 1-nitropropane, 2-nitropropane, 2-nitrobutane, 2-nitrooctane, nitrocyclohexane, and ethyl  $\alpha$ -nitrocaproate.<sup>17</sup>

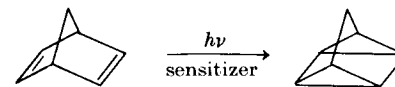
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2. Chemistry Department, Vanderbilt University, Nashville, Tennessee 37203.
3. Chemistry Department, Duke University, Durham, North Carolina 27706 (deceased January 6, 1970).
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## QUADRICYCLANE

(Tetracyclo[3.2.0.0.<sup>2,7</sup>0<sup>4,6</sup>]heptane)



Submitted by CLAIBOURNE D. SMITH<sup>1</sup>

Checked by A. J. TAGGI and J. MEINWALD

### 1. Procedure

In a Hanovia 550-watt immersion photochemical reactor (Note 1) equipped with a magnetic stirrer and water condenser (Note 2) are placed 1 l. of diethyl ether, 180 g. (1.96 moles) of bicyclo[2.2.1]hepta-2,5-diene (Note 3), and 8 g. of acetophenone. The system is flushed briefly with a stream of nitrogen and then irradiated for about 36–48 hours (Note 4). After irradiation, the ether is removed by distillation through a 20-cm. Vigreux column (Note 5). The residue, a clear liquid weighing about 185 g., is distilled through a spinning-band column under reduced pressure (Note 6). Quadricyclane is obtained as a colorless liquid, b.p. 70° (200 mm.). The yield is 126–145 g. (70–80%) (Note 7).

### 2. Notes

1. The reactor, manufactured by the Hanovia Division of Engelhard Industries, consists of a water-jacketed Pyrex well through which a stream of water is continuously passed. The well is placed in an appropriately shaped flask containing the solution to be irradiated.<sup>2</sup> The essentially cylindrical flask is equipped with a side arm near the top which is connected to a water-cooled condenser. There should be sufficient clearance between the bottom of the well and the flask to allow a magnetic stirring bar. The flask is so designed that the liquid level is above the top of the lamp.

2. A source of nitrogen is attached to the top of the condenser to protect the system from oxygen. The condenser serves as a safeguard in case the temperature of the system exceeds the boiling point of the solvent.

3. Bicyclo[2.2.1]hepta-2,5-diene was obtained from Shell Chemical Company and can be used as supplied. However, if the diene is distilled it should be used at once. The uninhibited diene may form a white, insoluble polymer or peroxide if allowed to stand in the presence of air and light. The use of undistilled diene results in a slightly lower yield of quadricyclane. The checkers used bicyclo[2.2.1]hepta-2,5-diene supplied by the Aldrich Chemical Company, Inc. This was distilled prior to use to give a pure sample, b.p. 89–90.5°,  $n_{D}^{26.5}$  1.4680.

4. Other sensitizers (acetone; benzophenone) can be used with slightly reduced yields. The reaction may be monitored by removing aliquots and analyzing by gas chromatography or n.m.r. For gas chromatography analysis a 2-m. column containing 20% by weight of 1,2,3-tris(2-cyanoethoxy)propane suspended on Gas Chrome R (60–80 mesh) is used at a temperature of 75° with a flow rate of 85 ml./minute of helium. The retention time for quadricyclane is 5.2 minutes. For n.m.r. analysis the disappearance of the absorption of the olefinic protons at 6.75 p.p.m. is followed.

Lower wattage lamps can be used, although the irradiation time would be somewhat longer. The checkers found this reaction to be almost complete in about half this time; lamp age and other similar factors will cause appreciable variation in the irradiation time required.

5. Rapid distillation of the solvent may slightly reduce the yield of product.

6. The only volatile impurity at this point is bicyclo[2.2.1]hepta-2,5-diene. If the irradiation has been carried out for a sufficient period of time, the amount of diene present is less than 2%. Distillation through an efficient column will remove most of the diene [bicyclo[2.2.1]hepta-2,5-diene, b.p. 91° (760 mm.), 51° (200 mm.)]. Traces of acid<sup>3</sup> and noble metal ions and complexes<sup>4</sup> may cause quadricyclane to isomerize to the diene. The checkers used a 60-cm. Teflon-coated spinning-band column

available from Nester-Faust Corporation. The submitter used a similar 43-cm. column.

7. The checkers found  $n_{D}^{26}$  1.4830 (lit.<sup>5</sup>  $n_{D}^{26.5}$  1.4830) for the distillate. The n.m.r. spectrum<sup>3</sup> shows two peaks at 1.41 (6H) and 2.00 p.p.m. (2H). No olefinic absorption was detectable. The infrared spectrum (carbon tetrachloride solution) shows three unusually well-resolved bands in the C–H stretching region at 3069, 2929, and 2852 cm.<sup>-1</sup>.

### 3. Discussion

Quadricyclane may be prepared by direct irradiation of bicyclo[2.2.1]hepta-2,5-diene<sup>3</sup> and 2,3-diazatetracyclo[4.3.0.0.<sup>4,8</sup>-0<sup>7,9</sup>]non-2-ene<sup>6</sup> or by photosensitized isomerization of bicyclo[2.2.1]hepta-2,5-diene.<sup>5,7</sup> Several substituted quadricyclanes have been prepared by direct irradiation<sup>8–11</sup> and by photosensitization.<sup>12–14</sup> The procedure described above can be used to isomerize substituted bicycloheptadienes to the corresponding quadricyclanes when traces of sensitizers can be conveniently removed or their presence does not interfere with further use of the quadricyclane.

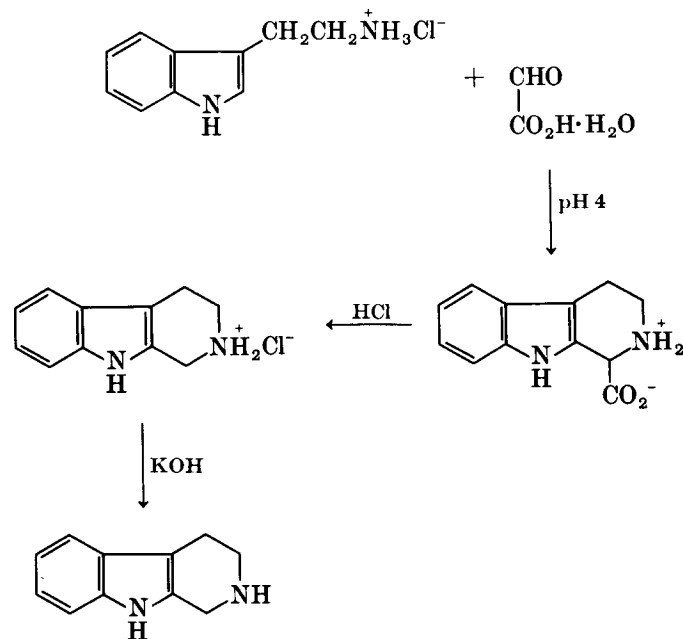
Quadricyclane is a highly strained and reactive compound. It reacts readily with acetic acid to give a mixture of nortricycyl acetate and *exo*-norbornyl acetate and with bromine to yield a mixture of 2,6-dibromonortricycene and *exo*-5-*anti*-7-dibromonorbornene.<sup>3</sup> Quadricyclane undergoes cycloaddition reactions with a variety of dienophiles to give 1:1 adducts.<sup>15</sup>

1. Contribution No. 1222 from the Central Research Department, E. I. du Pont de Nemours & Co. (Inc.), Experimental Station, Wilmington, Delaware 19898. [Present address, Fabrics and Finishes Department, E. I. du Pont de Nemours & Co. (Inc.), Marshall Laboratory, Philadelphia, Pennsylvania 19146.]
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### 1,2,3,4-TETRAHYDRO- $\beta$ -CARBOLINE

(9H-Pyrido[3,4-b]indole, 1,2,3,4-tetrahydro-)



Submitted by BENG T. HO and K. E. WALKER<sup>1</sup>  
 Checked by S. TEITEL, J. O'BRIEN, and A. BROSSI

#### 1. Procedure

In a 1-l. Erlenmeyer flask, 25 g. (0.13 mole) of tryptamine hydrochloride (Note 1) is dissolved with stirring in 400 ml. of water by warming on a steam bath to approximately 45°. After

cooling to room temperature, a solution of 13.2 g. (0.14 mole) of glyoxylic acid monohydrate (Note 2) in 30 ml. of water is added followed by the slow addition (about 3 minutes) of a cooled solution of 7.05 g. (0.126 mole) of potassium hydroxide in 35 ml. of water (Note 3). Precipitation of tetrahydro- $\beta$ -carboline-1-carboxylic acid takes place during the addition of the potassium hydroxide solution or soon thereafter. After stirring at ambient temperature for 1 hour, the solid is collected on a filter and washed thoroughly with 100 ml. of water. The damp filter cake is transferred to a 1-l. beaker, suspended in 240 ml. of water and 34 ml. of concentrated hydrochloric acid is slowly added (Note 4) with stirring. The mixture is boiled on a hot plate for 30 minutes, and then an additional 35 ml. of concentrated hydrochloric acid is added. Heating is continued for another 15 minutes, and the resulting solution is allowed to cool to room temperature. The precipitated hydrochloride salt is collected on a filter and washed with 30 ml. of water. The product is dissolved with stirring in 400 ml. of water by warming on a steam bath to approximately 55°, and the solution is adjusted to pH 12 with 20% aqueous potassium hydroxide (approximately 50 ml. is required). After cooling to room temperature, the product is collected by suction filtration, washed with 400 ml. of water and dried in a vacuum desiccator over phosphorus pentoxide. The yield of 1,2,3,4-tetrahydro- $\beta$ -carboline is 17.0–17.6 g. (78–80%); m.p. 204–205° (Note 5); n.m.r. spectrum (dimethylsulfoxide-*d*<sub>6</sub>): 2.70 (triplet, 2H, CH<sub>2</sub>), 2.72 (singlet, 1H, NH), 3.00 (triplet, 2H, NCH<sub>2</sub>), 3.85 (singlet, 2H,  $\geq$ CCH<sub>2</sub>N), 6.80–7.50 (multiplet, 4H, aromatic H), and 10.53 p.p.m. (singlet, 1H, NH).

#### 2. Notes

1. The checkers used tryptamine hydrochloride (m.p. 253–255°) purchased from Regis Chemical Company.

2. Glyoxylic acid monohydrate is available from Pierce Chemical Company.

3. The resulting solution should have a pH between 3.5 and 4.0; if not, it should be adjusted with either potassium hydroxide or hydrochloric acid solution.

4. If all the hydrochloric acid solution is added at once, foaming makes the reaction unmanageable.

5. The melting point agrees with that of the literature<sup>3</sup> and is unchanged on recrystallization of the product from ethanol.

### 3. Discussion

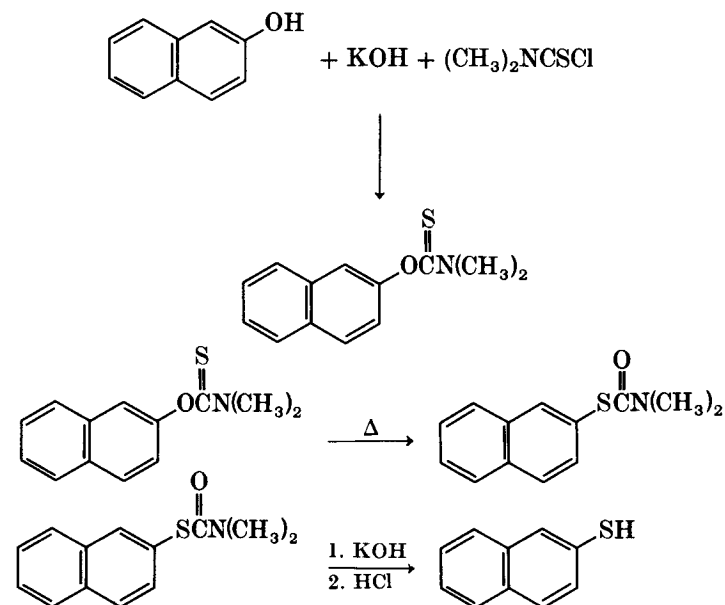
1,2,3,4-Tetrahydro- $\beta$ -carboline has been prepared by the condensation of tryptamine with formaldehyde in the presence of sulfuric acid<sup>2</sup> and has also been obtained as a by-product in the acid-catalyzed esterification of 1,2,3,4-tetrahydro- $\beta$ -carboline-1-carboxylic acid.<sup>3</sup>

The described two-step procedure is uncomplicated and can be carried out in 1 day to give in good yield a product that does not require any further purification. This procedure has been used for the preparation of 3-methyl-, 9-methyl-, and 6-methoxy-1,2,3,4-tetrahydro- $\beta$ -carboline<sup>4</sup> and has been modified to obtain 9-phenyl-1,2,3,4-tetrahydro- $\beta$ -carboline.<sup>5</sup> The method is generally applicable to the preparation of other 1-unsubstituted tetrahydro- $\beta$ -carbolines providing the 1-carboxylic acid precursor is not insoluble in the hot acid used to effect decarboxylation.

Reviews of the chemistry of the carbolines have been published.<sup>6,7</sup>

## THIOPHENOLS FROM PHENOLS: 2-NAPHTHALENETHIOL

### (2-Naphthalenethiol)



Submitted by MELVIN S. NEWMAN and FREDERICK W. HETZEL<sup>1</sup>  
 Checked by W. SCHILLING, R. KEESE, and A. ESCHENMOSER

### 1. Procedure

A. *O*-2-Naphthylthiodimethylthiocarbamate. A solution prepared by dissolving 21.6 g. (0.15 mole) of 2-naphthol (Note 1) in 100 ml. of water containing 8.4 g. (0.15 mole) of potassium hydroxide is cooled below 10° in a 500-ml. three-necked flask equipped with a stirrer, a thermometer, and a 125-ml. addition funnel. A solution of 24.8 g. (0.20 mole) of dimethylthiocarbamyl chloride (Note 2) in 40 ml. of dry tetrahydrofuran (Note 3) is added during 20–30 minutes to the stirred solution at such a rate that the temperature never exceeds 12°. After the addition is complete, the cooling bath is removed and stirring is continued for 10 minutes.

1. Texas Research Institute of Mental Sciences, Texas Medical Center, Houston, Texas 77025.
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The reaction mixture is made alkaline with 50 ml. of 10% potassium hydroxide solution and is shaken three times with 100-ml. portions of benzene. The organic layers are combined, washed with a saturated sodium chloride solution, and dried by filtration through anhydrous magnesium sulfate. The solvent is removed by distillation to give the crude product that is crystallized from 75 ml. of absolute methanol to yield 23.5–25.2 g. (68–73%) of colorless crystals of O-2-naphthyldimethylthiocarbamate, m.p. 90–90.5°.

B. 2-Naphthalenethiol. In a 250-ml. flask, fitted with a diffusion tube<sup>2</sup> and swept with nitrogen, is placed 23.1 g. (0.10 mole) of O-2-naphthyldimethylthiocarbamate (Note 4). The flask is heated at 270–275° for 45 minutes in a salt bath (Note 5). After cooling, a solution of 8.4 g. (0.15 mole) of potassium hydroxide in 10 ml. of water and 75 ml. of ethylene glycol is added to the flask. The diffusion tube is replaced by a condenser, and the mixture is heated at reflux for 1 hour (Note 6). The cooled reaction mixture is poured onto 150 g. of ice. After the ice has melted, the mixture is shaken two times with 150-ml. portions of chloroform. The chloroform layers are discarded, and the aqueous layer is cautiously acidified with concentrated hydrochloric acid (Note 7) and shaken three times with 75-ml. portions of chloroform. The organic layers are combined and dried by filtration through anhydrous magnesium sulfate. The solvent is removed by distillation to yield 13–15 g. of crude product. Distillation yields 10.3–12.8 g. (71–80%) of pure 2-naphthalenethiol, b.p. 92–94° (0.4 mm.), m.p. 80–81° (Note 8).

## 2. Notes

1. Practical 2-naphthol, obtained from Matheson Coleman and Bell, was recrystallized twice from benzene to m.p. 123–124°.

2. Dimethylthiocarbamyl chloride can be prepared as described in *Org. Syn.*, Coll. Vol. 4, 310 (1963), or by rapidly adding 740 g. (10.5 moles) of chlorine dissolved in 3 l. of carbon tetrachloride to a stirred refluxing suspension of 2400 g. (10 moles) of tetramethylthiram disulfide (Note 9) in 5 l. of carbon tetrachloride. After the addition is complete, approximately one-half of

the solvent is removed by distillation. The reaction mixture is cooled, filtered to remove the precipitated sulfur, and further concentrated. The residue is distilled to yield 1980 g. (80%) of dimethylthiocarbamyl chloride, b.p. 65–68° (0.2 mm.).

3. See *Org. Syn.*, 46, 105 (1966) for a warning note regarding the purification of tetrahydrofuran.

4. Crude O-2-naphthyldimethylthiocarbamate should not be used in this step as the yield is markedly decreased.

5. The salt bath is described in *Org. Syn.*, Coll. Vol. 4, 498 (1963).

6. The hydrolysis should be performed in a hood because of the vigorous evolution of dimethylamine.

7. The dilute acid solution should be added slowly since foaming results from the evolution of carbon dioxide.

8. Purification can be accomplished by recrystallization from methanol, but the overall yield of pure material is 65–70%.

9. Tetramethylthiram disulfide was obtained from the Pennwalt Corporation.

## 3. Discussion

The procedure described is a good general method<sup>3</sup> for obtaining a thiophenol from the respective phenol. It employs three steps: conversion of a phenol to the O-aryl dialkylthiocarbamate by treatment with dialkylthiocarbonyl chloride; pyrolysis of the O-aryl dialkylthiocarbamate to the S-aryl dialkylthiocarbamate; and hydrolysis of the latter to the aryl mercaptan.

Previous preparations of 2-naphthalenethiol have included reduction of 2-naphthylsulfonyl chloride with zinc and acid<sup>4,5</sup> or phosphorus and iodine.<sup>6,7</sup> Alternatively, 2-naphthyldiazonium chloride has been converted to the thiol using potassium ethyl xanthate and sodium carbonate.<sup>8</sup>

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8. When prepared as described, the oxonium salt is stable, nonhygroscopic, and may readily be handled in the air for short periods of time. A sample kept in a desiccator over Drierite for 1 month at  $-20^\circ$  showed no change in melting point, and batches stored in this manner for over a year have been successfully used for alkylations.

### 3. Discussion

Trialkyloxonium salts were first discovered by Meerwein,<sup>2</sup> who also investigated much of their chemistry. A discussion of the literature prior to 1963 has been published.<sup>5</sup> Simple trialkyloxonium cations which have been prepared, other than trimethyl, include triethyl,<sup>6</sup> tri-*n*-propyl,<sup>7</sup> and tri-*n*-butyl.<sup>8</sup> Most commonly the anions have been tetrafluoroborate or hexachloroantimonate. Methods used to prepare trimethyloxonium tetrafluoroborate, which are typical of the class as a whole, include the reaction of boron trifluoride with epichlorohydrin in the presence of dimethyl ether,<sup>2,4,9</sup> the reaction of dimethyloxonium tetrafluoroborate with diazomethane or diazoacetic ester,<sup>10</sup> and the alkylation of dimethyl ether by triethyloxonium tetrafluoroborate<sup>3</sup> or dimethoxycarbonium tetrafluoroborate.<sup>11</sup> Several of these reactions involve the initial formation of a mixed oxonium ion  $[R_1R_2OCH_3]^+$ , which then methylates dimethyl ether to produce  $R_1R_2O$  and the trimethyloxonium ion. Of the available procedures, the one described here is probably the most convenient, involving as it does a single-step preparation from inexpensive, commercially available, and nonhazardous reagents. Under the proper conditions (Note 8), the resulting product has storage properties comparable to those of the less-accessible trimethyloxonium 2,4,6-trinitrobenzene-sulfonate.<sup>12</sup>

The trialkyloxonium salts are powerful alkylating agents. Trimethyl- and triethyloxonium tetrafluoroborates, in particular, have been widely employed for methylation and ethylation of sensitive or weakly nucleophilic functional groups. Alkylations of over 50 such functional groups have been reported in the literature. Examples include amides,<sup>4,7,13-15</sup> lac-

tams,<sup>4,15-18</sup> sulfides,<sup>2,19</sup> nitro compounds,<sup>9</sup> enols and enolates,<sup>2,20</sup> ethers,<sup>3,7,21</sup> phenols,<sup>2</sup> sulfoxides,<sup>2,7</sup> amine oxides,<sup>2,7,22</sup> carboxylic acids,<sup>2</sup> lactones,<sup>2,4</sup> ketones,<sup>2,15</sup> metal carbonyls,<sup>11,23</sup> thiophenes,<sup>24</sup> and phosphonitriles.<sup>25</sup> Oxonium salts have also been advantageously employed as quaternizing agents for a variety of heterocyclic amines.<sup>26-33</sup> In this way the first diquaternary salts of several heterocyclic diazines have been prepared,<sup>29,30</sup> as have reagents for peptide synthesis,<sup>32,33</sup> for the synthesis of polycyclic ketones,<sup>31</sup> and for cyanine dyes.<sup>27</sup>

One of the major advantages of oxonium salts is that alkylations can be effected under reaction conditions that are generally much milder than those necessary with the more conventional alkyl halides or sulfonates. Triethyloxonium tetrafluoroborate, for example, has usually been employed at room temperature in dichloromethane or dichloroethane solution. Occasionally chloroform<sup>16,22</sup> or no solvent at all<sup>4,20</sup> is used. Difficult alkylations can be effected in refluxing dichloroethane.<sup>29,30</sup> The less soluble trimethyloxonium tetrafluoroborate has been used as a suspension in dichloromethane or dichloroethane, or as a solution in nitromethane or liquid sulfur dioxide. Reports of alkylations in water<sup>23</sup> and trifluoroacetic acid<sup>21</sup> have also appeared. Direct fusion with trimethyloxonium tetrafluoroborate has succeeded in cases where other conditions have failed.<sup>25,30</sup>

Alkylations by oxonium salts have added several new weapons to the synthetic chemist's armamentarium. For example, the O-alkylated products from amides  $[R_1C(OR)=NR_2R_3]^+$  ( $R = CH_3$  or  $C_2H_5$ ) may be hydrolyzed under mild conditions to amines and esters,<sup>14,34</sup> reduced to the amines  $R_1CH_2NR_2R_3$  by sodium borohydride,<sup>13</sup> converted to amide acetals  $R_1C(OR)_2NR_2R_3$  by alkoxides,<sup>4,15</sup> and (for  $R_3 = H$ ) deprotonated to the imino esters  $R_1C(OR)=NR_2$ .<sup>16-18</sup> Amide acetals and imino esters are themselves in turn useful synthetic intermediates. Indeed, oxonium salts transform the rather intractable amide group into a highly reactive and versatile functionality, a fact elegantly exploited in recent work on the synthesis of corrins.<sup>34</sup>

Other reagents which approach or exceed the oxonium salts in alkylating ability include dialkoxycarbonium ions,<sup>35</sup> alkyl

trifluoromethanesulfonates,<sup>36</sup> alkyl fluorosulfonates,<sup>37</sup> dialkyl-halonium ions,<sup>38</sup> and alkyl halides in the presence of silver salts.<sup>24,36,39</sup> In terms of availability, stability, and freedom from hazards,<sup>24</sup> however, oxonium salts often appear to be the reagents of choice. When either methylation or ethylation is acceptable, methylation may be preferable. Thus triethyloxonium tetrafluoroborate must be stored under ether and handled in a dry box,<sup>6</sup> whereas the trimethyl salt can be stored solvent-free in the freezing compartment of a refrigerator and dispensed in the open atmosphere. Moreover, while information on the relative alkylating ability of the oxonium salts is not extensive, a few cases have been reported in which trimethyloxonium tetrafluoroborate effected alkylations which the triethyl analog did not.<sup>19,30</sup> The trimethyloxonium salt, therefore, appears to be the more potent alkylating agent.

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## HAZARD NOTE

Very high carcinogenic activity has been reported for bis-(chloromethyl) ether when administered to rats by inhalation and by subcutaneous injection. This compound should be handled with great care.

Reported by B. L. Van Duuren, A. Sivak, B. M. Goldschmidt, C. Katz, and S. Melchionne, *J. Nat. Cancer Inst.*, **43**, 481 (1969).

di-(*p*-CHLOROPHENYL)ACETIC ACID<sup>2</sup>

## CORRECTION

In the first line of Note 5, p. 271, 1,1-di-(*p*-chlorophenyl)-ethylene should read

1,1-di-(*p*-chlorophenyl)-2,2-dichloroethylene.

Reported by B. Stavric and G. A. Neville, *J. Ass. Offic. Anal. Chem.*, **53**, 1270 (1970):

<sup>1</sup> *Org. Syn.*, Coll. Vol. **4**, 101 (1963).

<sup>2</sup> *Org. Syn.*, Coll. Vol. **3**, 271 (1955).

## INDEX

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for previous volumes see Collective Volumes 1 through 5.)

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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