

Experimental

Ethyl 2-Tridecanoyltridecanoate.—A suspension of finely divided sodium (5.75 g. or 0.25 g. atom) in 60 ml. of xylene was treated with 11.5 g. (0.25 mole) of absolute ethanol and the mixture heated under reflux until all the sodium had disappeared. The solvent was removed under reduced pressure and 180 g. (0.54 mole) of ethyl tridecanoate⁴ added to the dry powdered sodium ethoxide.

The reaction mixture was heated to 130° at 14 mm. pressure for four hours, during which time all ethanol was removed. Excess dilute acetic acid was added to the cooled residue which caused an oily layer to appear on the surface of the mixture, and a gelatinous material adhered to the bottom of the flask. The oily layer was separated and recrystallized from methanol to give 80 g. (67% yield) of ketoester melting at 32–33°.

Anal. Calcd. for C₂₈H₅₄O₃: C, 76.8; H, 12.3. Found: C, 76.9; H, 12.3.

The gelatinous material from the above reaction mixture was separated and washed thoroughly with dilute acetic acid. The product was recrystallized from methanol to yield 4.5 g. of solid which melted at 73–74°. The melting point of 13-pentacosanone is reported⁵ as 73–74° and Briese and McElvain⁶ have reported the tendency of long chain β-ketoesters to undergo loss of carbethoxy group on distillation. It was considered likely that part of the β-ketoester had been converted to 13-pentacosanone during the four-hour heating period of the Claisen condensation.

A semicarbazone of the 13-pentacosanone was prepared in the usual manner and melted at 61–62°.

Anal. Calcd. for C₂₅H₅₀N₂O: N, 9.90. Found: N, 9.93.

Clemmensen Reduction of Ethyl 2-Tridecanoyltridecanoate.—A mixture of 43 g. (0.1 mole) of ethyl 2-tridecanoyltridecanoate, 1 l. of commercial absolute ethanol and 262 g. of zinc amalgam was saturated with dry hydrogen chloride and heated under reflux for 20 hours. The cooled mixture was saturated again with hydrogen chloride and refluxed for a second 20-hour period. The liquid phase was separated and cooled and the precipitated solid separated. The solid was recrystallized from methanol to yield 39 g. of product melting at 52–54°. Eighteen grams of this product was recrystallized several times from petroleum ether and two times from ethyl ether to give 14 g., corresponding to an 87% yield, of product melting at 53.5–55°. The melting point of pentacosane has been reported⁷ as 53.5–54°.

A small amount of the 13-pentacosanone, obtained as described above, was subjected to Clemmensen reduction to give pentacosane melting at 54–55°. A mixed melting point between this material and the 53.5–55° melting product obtained above showed no depression.

(4) A. H. Blatt, "Organic Syntheses," Coll. Vol. II. John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 292–293.

(5) R. N. Meals, *J. Org. Chem.*, **9**, 211 (1944).

(6) R. Briese and S. M. McElvain, *THIS JOURNAL*, **55**, 1697 (1933).

(7) W. Cluud, *Ber.*, **52**, 1039 (1919).

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RECEIVED JUNE 15, 1951

The Preparation of Isochromans

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The purpose of this note is to report a method for the synthesis of isochroman¹ (V) and 3-phenylisochroman (VI) and to display the application of these and related procedures to the synthesis of substituted isochromans.

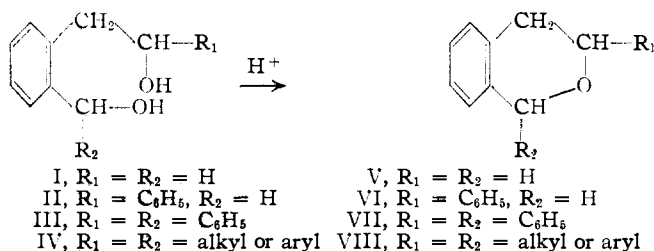
Isochromans form readily *via* the acid-catalyzed dehydration of the appropriate glycol.^{2,3} Homo-

(1) Our work, carried out independently, confirms the method of preparation of isochroman recently published by F. L. Anderson and F. G. Holliman, *J. Chem. Soc.*, 1037 (1950).

(2) W. G. Young and S. Siegel, *THIS JOURNAL*, **66**, 354 (1944).

(3) S. Siegel, S. Coburn and D. R. Levering, *ibid.*, **73**, 3163 (1951).

phthalic acid, which is now easily obtained,⁴ provides a convenient starting point for the preparation of these glycols. Thus, the reduction with lithium aluminum hydride of homophthalic anhydride or methyl homophthalate¹ yields homo-



phthalyl alcohol (I) which can in turn be converted to isochroman (V). Or the anhydride may be condensed with benzene^{5,6} to form *o*-phenacylbenzoic acid whose lactone, 3-phenylisocoumarin,⁵ may be reduced to the glycol II, which can yield 3-phenylisochroman (VI).

A further extension of this synthesis follows from the addition of phenylmagnesium bromide to 3-phenylisocoumarin which yields 2-phenacylbenzophenone. The preparation of 1,3-diphenylisochroman (VII) by this procedure was described earlier.³

Perhaps the simplest way to obtain 1,3-dialkyl- or 1,3-diarylisochromans (VIII) is through the dehydration of the "abnormal" product, a glycol (IV), obtained in the reaction of benzylmagnesium chloride with aldehydes.^{2,3,7}

Isochroman is readily oxidized when exposed to the air and a crystalline substance, apparently a peroxide, is easily isolated. 3-Phenylisochroman is also sensitive to oxidation, although 1,3-diphenylisochroman is less reactive.

Experimental⁸

Homophthalyl Alcohol.—Homophthalyl alcohol was prepared by the reduction of homophthalic anhydride according to the method of Nystrom and Brown⁹ which is used for compounds with a low solubility in ether. The product was isolated in a manner described previously³ and was distilled *in vacuo*. From 20 g. of the anhydride was obtained 8 g. of the alcohol, b.p. 164–165° (2 mm.); n_D^{20} 1.5556.

Isochroman.—A mixture of homophthalyl alcohol (2.6 g.) and potassium acid sulfate (1 g.) was heated to 45° for 20 minutes. The oily residue was distilled; 1.2 g., b.p. 67–69° (2 mm.); n_D^{20} 1.5422.

2-(2-Hydroxy-2-phenylethyl)-phenylcarbinol (II).—3-Phenylisocoumarin (2 g.) was reduced with LiAlH₄ in the usual way.⁹ The product was distilled at 1 × 10⁻⁴ mm. (105° bath temperature) in a short path still; 1.22 g., n_D^{20} 1.5986.

Anal. Calcd. for C₁₅H₁₆O₂: C, 78.9; H, 7.08. Found: C, 79.16; H, 6.75.

3-Phenylisochroman.—To a solution of the glycol (II) in glacial acetic acid was added a few drops of sulfuric acid. Water was added to decrease the solubility of the product and the crystalline 3-phenylisochroman formed. The product was recrystallized from acetone; m.p. 114–115°.

Anal. Calcd. for C₁₅H₁₄O: C, 85.67; H, 6.71. Found: C, 86.27; H, 6.17.

(4) (a) C. C. Price, *Org. Syntheses*, **22**, 61 (1942); (b) Buck, O. Grummitt and Egan, *ibid.*, **29**, 49 (1949).

(5) C. Graebe and F. Trumphy, *Ber.*, **31**, 377 (1898).

(6) See also A. Horeau and J. Jacques, *Bull. Soc. Chim.*, **15**, 53 (1948).

(7) S. Siegel, W. M. Boyer and R. R. Jay, *THIS JOURNAL*, **73**, 3237 (1951).

(8) Elementary analysis by Micro-Tech Laboratories, Skokie, Illinois.

(9) R. F. Nystrom and W. G. Brown, *THIS JOURNAL*, **69**, 1197 (1947).

Peroxide of Isochroman.—The viscosity of isochroman increased markedly when it was allowed to stand at room temperature in a glass vessel for several days. A white crystalline material formed slowly and it was purified by recrystallization from ethyl ether in which it is moderately soluble. The solid is only slightly soluble in alcohol. The compound melts sharply with decomposition at 147° and decomposes slowly at 78° *in vacuo*. Isochroman is probably oxidized at the 1-position.

Anal. Calcd. for C₁₈H₁₈O₄: C, 72.41; H, 6.08. Found: C, 72.32; H, 6.15.

3-Phenylisochroman is also sensitive to air and is consequently troublesome to purify. However, 1,3-diphenylisochroman is apparently unreactive. A sample of this compound was unaltered after storage for two years in a screw cap vial.

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RECEIVED JUNE 11, 1951

A New Synthesis of Mescaline

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The cactus alkaloid, mescaline, β -(3,4,5-trimethoxyphenyl)-ethylamine, has been studied for some years, because of its most interesting effects on the psychic states of human subjects. Since the elucidation of the chemical structure of the alkaloid through the synthesis by Späth,¹ a few other methods of preparation have been published.²⁻⁷ A simple synthesis utilizing lithium aluminum hydride is presented in this report. The synthesis may be outlined as follows: gallic acid \rightarrow 3,4,5-trimethoxybenzoic acid \rightarrow methyl ester of 3,4,5-trimethoxybenzoic acid \rightarrow 3,4,5-trimethoxybenzyl alcohol \rightarrow 3,4,5-trimethoxybenzyl chloride \rightarrow 3,4,5-trimethoxyphenylacetone nitrile \rightarrow mescaline.

Experimental

Methyl Ester of 3,4,5-Trimethoxybenzoic Acid.—To a solution prepared from 100 g. of 3,4,5-trimethoxybenzoic acid⁸ (0.47 mole), 20 g. of sodium hydroxide, 55 g. of sodium carbonate and 300 ml. of water is added, with stirring, 94 ml. of methyl sulfate (0.94 mole) during the course of 20 minutes. The reaction mixture is refluxed for one-half hour. The crude ester (65 g., 61%) precipitates from the cold mixture. From the filtrate 38 g. of starting material is recovered upon acidification with diluted hydrochloric acid. The ester is further purified by solution in the minimum amount of methanol and treatment with norite. Usually it is necessary to repeat this treatment to obtain a colorless crystalline product that melts at 80–82°. Semmler,⁹ who employed a different process, reported m.p. 83–84°.

3,4,5-Trimethoxybenzyl Alcohol.—To a suspension of 4.6 g. (0.12 mole) of lithium aluminum hydride in 200 ml. of anhydrous ether is added, in the course of 30 minutes, a solution of 22.6 g. (0.1 mole) of the methyl ester of 3,4,5-trimethoxybenzoic acid in 300 ml. of ether. The solid which forms is carefully decomposed first with 50 ml. of ice-water. After decantation of the ether, 250 ml. of ice-cold 10% sulfuric acid is added. The product is extracted with 150 ml. of ether. The combined extracts, after drying over sodium sulfate, are freed of ether and the residue distilled; b.p. 135–137° (0.25 mm.); yield 14.7 g. (73%). This com-

pound was obtained by a different method by Marx¹⁰; b.p. 228° (25 mm.).

3,5-Dinitrobenzoate of 3,4,5-Trimethoxybenzyl Alcohol.—This derivative was prepared with 3,5-dinitrobenzoyl chloride and recrystallized from ethanol. The yellow diamond-shaped crystals melt at 143–144°.¹¹

Anal. Calcd. for C₁₇H₁₈O₉N₂: C, 52.04; H, 4.11. Found: C, 52.31; H, 4.21.

3,4,5-Trimethoxybenzyl Chloride.—A mixture of 25 g. of 3,4,5-trimethoxybenzyl alcohol and 125 ml. of ice-cold concentrated hydrochloric acid is shaken vigorously until a homogeneous solution is obtained. In a few minutes a turbidity develops, followed by a heavy precipitation of gummy product. After 4 hours and dilution with 100 ml. of ice-water, the aqueous layer is decanted and extracted with three 50-ml. portions of benzene. Then the gummy organic residue is dissolved in the combined benzene extracts. The benzene solution is washed with water and dried over sodium sulfate.

The benzene solution is transferred to a distilling flask and the benzene is removed under diminished pressure. The red semi-solid residue is suspended in a small amount of ice-cold ether and filtered through a chilled funnel. The crystalline product, after washing with small portions of cold ether, weighs 9.7 g. The combined filtrates on standing in refrigerator yield more crystals. The total yield is 13.0 g. (48%). After four recrystallizations from benzene, colorless needles are obtained; m.p. 60–62°.

Anal. Calcd. for C₁₀H₁₀O₃Cl: C, 55.42; H, 6.05. Found: C, 55.55; H, 6.13.

This compound is extremely soluble in ether, alcohol and acetone, but slightly soluble in petroleum ether. Standing at room temperature for a few weeks causes the crystals to turn into a red semi-solid. An alcoholic solution of pure material gives an instantaneous precipitation with alcoholic silver nitrate.

3,4,5-Trimethoxyphenylacetone nitrile.—A mixture of 9 g. of potassium cyanide in 35 ml. of water and 60 ml. of methanol and 9.7 g. of 3,4,5-trimethoxybenzyl chloride is heated for 10 minutes at 90°. The solvents are partially removed under diminished pressure. The residue is then extracted with 90 ml. of ether in three portions. The combined extracts are washed with water and dried over sodium sulfate. After the removal of the drying agent the ether solution is warmed on a steam-bath and the ether is removed with a stream of air. On chilling, the residue yields scale-like crystals. Recrystallization from ether gives rectangular prism; yield 2.5 g. (27%); m.p. 76–77°. Baker and Robinson¹² reported a melting point of 77° for this compound.

Mescaline.—In 150 ml. of anhydrous ether is suspended 0.85 g. of lithium aluminum hydride powder. With stirring, 2.0 g. of 3,4,5-trimethoxyphenylacetone nitrile in 150 ml. of anhydrous ether was added during the course of 15 minutes. After 15 minutes' stirring, 10 ml. of ice-water is dropped in carefully. Then a mixture of 10 g. of sulfuric acid in 40 ml. of water is added at a moderate rate. The aqueous layer is separated and treated with concentrated sodium hydroxide. The brown oil is extracted with three portions of 30 ml. each of ether. The combined extracts are washed once with water and dried over stick potassium hydroxide. To the decanted ether solution is added a mixture of 1 g. of sulfuric acid and 25 ml. of ether. The white precipitate is washed several times with ether; yield 1.2 g. (40%). After two recrystallizations from 95% ethanol, the colorless long thin plates soften at 172° and melt at 183°.

A sample of mescaline acid sulfate prepared from the natural source and kindly furnished by Dr. Seevers of the Department of Pharmacology softens at 170° and melts at 180°. The mixed melting point of above two samples is 181°. The picrate, prepared from the acid sulfate, melts at 217° (dec.), after three recrystallizations from ethanol. The chloroplatinate prepared from free base melts at 184–185°. Späth¹ gave the following melting points: sulfate, 183–186°; picrate, 216–218°; chloroplatinate, 187–188°.

Acknowledgment.—The author is indebted to Dr. P. A. S. Smith for generously making available the facilities of his laboratory in carrying

- (1) E. Späth, *Monatsh.*, **40**, 129 (1919).
- (2) K. H. Slotta and H. Heller, *Ber.*, **63B**, 3029 (1930).
- (3) H. Frisch and E. Waldmann, German Patent 545,853, July 3, 1930; *C. A.*, **26**, 3521¹ (1932).
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- (5) K. H. Slotta and G. Szyzka, *J. prakt. Chem.*, **137**, 339 (1933).
- (6) G. Hahn and H. Wassmuth, *Ber.*, **67**, 711 (1934).
- (7) G. Hahn and F. Rumpf, *ibid.*, **71B**, 2141 (1938).
- (8) A. H. Blatt, "Organic Syntheses," Coll. Vol. 1, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1946, p. 537.
- (9) F. W. Semmler, *Ber.*, **41**, 1774 (1908).

(10) M. Marx, *Ann.*, **263**, 254 (1891).

(11) All m.p.s. are uncorrected.

(12) Baker and R. Robinson, *J. Chem. Soc.*, 160 (1929).