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 $C_{18}H_{18}O_4$: 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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A New Synthesis of Mescaline

BY MAKEPEACE U. TSAO

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 → 3,4,5-trimethoxybenzoic acid → methyl ester of 3,4,5-trimethoxybenzoic acid → 3,4,5-trimethoxybenzyl alcohol → 3,4,5-trimethoxybenzyl chloride → 3,4,5-trimethoxyphenylacetonitrile → mescaline.

Experimental

Methyl Ester of 3,4,5-Trimethoxybenzoic Acid.—To a solution prepared from 100 g. of 3,4,5-trimethoxybenzoic acid[8] (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 compound was obtained by a different method by Marx[10]; 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 $C_{17}H_{16}O_9N_2$: 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 $C_{10}H_{13}O_3Cl$: 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-Trimethoxyphenylacetonitrile.—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 Robinson[12] 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-trimethoxyphenylacetonitrile 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°. Späth[1] gave the following melting points: sulfate, 183–186°; picrate, 216–218°; chloroplatinate, 187–188°.

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Preparation of 1-C^{14}-D-Xylose from 1-C^{14}-D-Glucose

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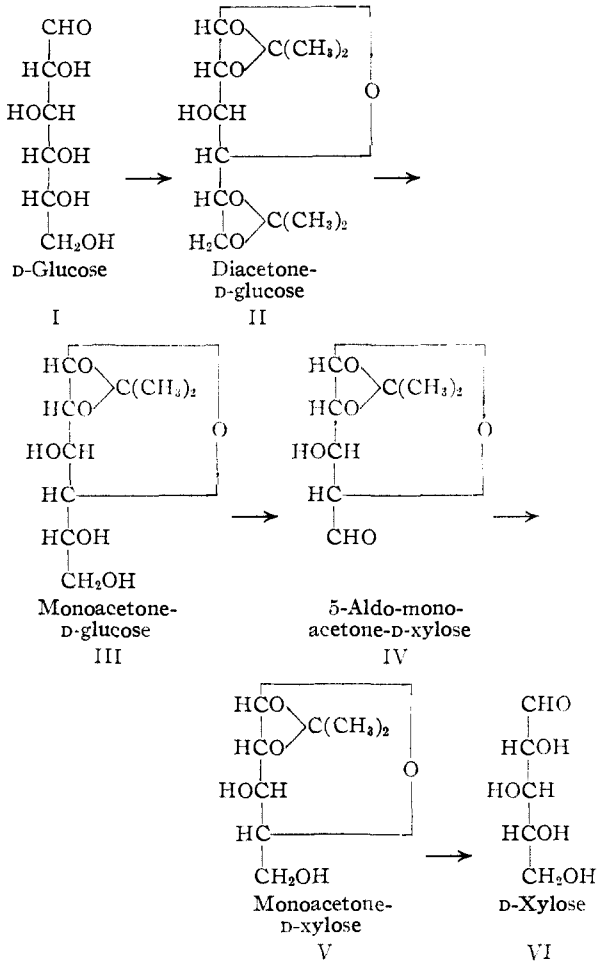
The development of methods for the isotopic labeling of sugars in the aldehydic carbon has supplied a valuable means of elucidating certain chemical and biochemical reactions that involve fragmentation of the sugar carbon chain. Either the nitromethane synthesis using C^{14}-nitromethane[1] or the cyanohydrin synthesis using C^{14}-cyanide,[2] which were first used to prepare 1-C^{14}-D-glucose and 1-C^{14}-D-mannose from D-arabinose, are generally applicable to the synthesis of aldehyde-labeled aldose sugars. In the pentose series, Rappoport and Hassid have described the preparation of 1-C^{14}-L-arabinose by application of the C^{14}-nitromethane synthesis to L-erythrose.[3]

Recently, 1-C^{14}-D-xylose has been employed in a study of the mechanism of fermentation of this aldopentose by *Lactobacillus pentosus*.[4] The preparation of aldehyde-labeled D-xylose by one of the two chain-lengthening synthetic methods would require as a starting material the tetrose sugar, D-threose. An alternate method, described herein, starts from 1-C^{14}-D-glucose and utilizes a sequence of reactions that eliminates carbon-6 from the glucose molecule and transforms the grouping at carbon-5 to a primary alcohol.

The well-known acetonation of D-glucose (I)[5] to 1,2;5,6-diisopropylidene-D-glucofuranose (diacetoneglucose) (II) and the controlled hydrolysis of the latter to 1,2-isopropylidene-D-glucofuranose,[6] (monoacetoneglucose) (III) have been improved recently[7] to provide excellent yields of III in solution.[8] The oxidative glycol cleavage of monoacetoneglucose leads to the substituted dialdehyde, 5-aldo-1,2-isopropylidene-D-xylofuranose (IV).[9] The reduction of the latter with hydrogen in the presence of Raney nickel produced the previously known[10] 1,2-isopropylidene-D-xylofuranose (V). Finally, mild acid hydrolysis of V removed the acetone substituent to give D-xylose (VI). The transformation of D-glucose to D-xylose by this reaction sequence has been accomplished, without the isolation of intermediates, in 55–60% yield.



The substituted dialdehyde, IV, is of interest in that its asymmetry is maintained only by virtue of the 1,2-ketal substituent. (Hydrolysis of the blocking acetone group would produce the *meso* compound, xylaric dialdehyde.) Similar preservation of asymmetry by substitution is a familiar and intrinsic feature of asymmetric glycerol chemistry.[11]

Experimental

1-C^{14}-D-glucose,[1] (630 ± 20 ct./min./mg.), was acetonated by the method of Bell[12] and the resulting diacetoneglucose hydrolyzed according to the directions of Coles, Goodhue and Hixon[13] to monoacetoneglucose. The latter, after recrystallization, was oxidized with aqueous sodium metaperiodate and the resulting 5-aldo-monoacetonexylose was reduced to monoacetonexylose as described below. The acetonated pentose was purified by distillation in a high vacuum and then hydrolyzed with dilute sulfuric acid to 1-C^{14}-D-xylose, m.p. 145–146°, $[\alpha]^{24}D$ 18.8° equil. in water (*c* 1.2). The isolation of the intermediates, especially monoacetoneglucose, leads to considerable losses and consequently the over-all yield of 1-C^{14}-D-xylose was only about 20%.

Subsequent to the radioactive preparation, experiments with non-radioactive D-glucose have led to the improved procedure described below. The directions of Mehltretter, *et al.*,[7] for the production of monoacetoneglucose in solution were employed and the isolation of all intermediate products was eliminated with a consequent increase in yield to 55–60% of D-xylose from D-glucose. The main loss in the fol-

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