The 2,3-di-*O*-toluene-*p*-sulphonate was prepared in a similar fashion from the *iso*propylidene derivative (0.1 gm.), pyridine (10 ml.), and toluene-*p*-sulphonyl chloride (1.0 gm.). The product was recrystallized from methanol, m.p. 145°C. Anal. Calc. for $C_{24}H_{30}O_{10}S_2$: C, 53.2; H, 5.6; OMe, 11.8. Found: C, 53.3; H, 5.6; OMe, 11.8.

*2,3-Di-O-benzoyl-4,6-O-isopropylidene-methyl-α-*D*-glucoside*

The *iso*propylidene derivative of methyl-α-D-glucoside (2.1 gm.) was dissolved in pyridine (30 ml.) and benzoyl chloride (5 ml.) added. The solution became warm and pyridine hydrochloride began to separate. After 12 hr., water (5 ml.) was added and the mixture poured onto ice. The 2,3-di-*O*-benzoyl derivative was isolated by extraction of the solution with chloroform. The product was recrystallized from acetone methanol. Yield: 2.8 gm., 70%; m.p. 131°C. Anal. Calc. for $C_{24}H_{26}O_8$: C, 65.2; H, 6.0. Found: C, 65.3; H, 6.1.

*Oxidation of 4,6-O-Isopropylidene-methyl-α-*D*-glucoside with Sodium Metaperiodate*

The substance (0.248 gm.) was dissolved in water (5 ml.), a solution of sodium *meta*periodate (5 ml., 0.25 *M*) added, and the change in optical rotation observed. $[\alpha]_D$ +92° (3 min.); +88° (4 min.); +71° (15 min.); +62° (25 min.); +46° (65 min.); +48° (120 min.); +57° (180 min.); +82° (20 hr.) constant value. At the stage of minimum optical rotation approximately one mole of periodate had been consumed per mole of sugar derivative.

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1. Ault, R. G., Haworth, W. N., and Hirst, E. L. J. Chem. Soc. 1012. 1935.
2. Irvine, J. C. and Scott, J. P. J. Chem. Soc. 103: 575. 1913.
3. Mellies, R. L., Mehltretter, C. L., and Rist, E. C. J. Am. Chem. Soc. 73: 294. 1951.
4. Mills, J. A. Chemistry & Industry, 633. 1954.
5. Mills, J. A. Advances in Carbohydrate Chem. 10: 1. 1955.

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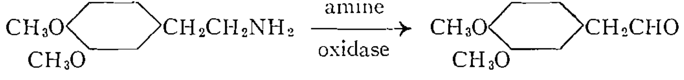
THE SYNTHESIS OF 3,4,5-TRIMETHOXYPHENYLACETALDEHYDE[1]

By J. G. Duff and J. M. Pepper

As part of a more general program of research concerned with a biochemical study of the hallucinogenic activity of mescaline (I), it was necessary to prepare 3,4,5-trimethoxyphenylacetaldehyde (II). If the primary action of this drug were the deamination by an amine oxidase:



I II

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[1] *This note constitutes part of a thesis submitted by J. G. Duff for the degree of Master of Science in Pharmacy, March, 1955.*

then the resulting aldehyde might be considered to show a similar if not even an enhanced activity.

One prior synthesis of this aldehyde has been reported, that by Mauthner (1) who obtained it by the ozonolysis of 3,4,5-trimethoxyallylbenzene. In this work the following alternative synthetic routes were followed:

1. 3,4,5-Trimethoxyallylbenzene was hydroxylated with cold potassium permanganate and the resulting diol was oxidized with either periodic acid or lead tetraacetate to produce the required aldehyde (II).

2. 3,4,5-Trimethoxybenzaldehyde was converted to the homoaldehyde (II) by the application of the Darzens glycidic ester condensation procedure.

From both syntheses the required 3,4,5-trimethoxyphenylacetaldehyde was obtained, after distillation, as a white crystalline solid, m.p. 39–40°C., although previously reported by Mauthner (1) to be an oil.

EXPERIMENTAL[2]

Method 1

3,4,5-Trimethoxyallylbenzene

4-Hydroxy-3,5-dimethoxyallylbenzene, which had been prepared from 2,6-dimethoxyphenol according to the method of Pearl (3), was methylated with dimethyl sulphate in alkali to produce 3,4,5-trimethoxyallylbenzene.

3-(3′,4′,5′-Trimethoxyphenyl)propanediol-1,2

The most satisfactory conditions found for the hydroxylation of 3,4,5-trimethoxyallylbenzene were as follows. 3,4,5-Trimethoxyallylbenzene (20.8 gm.) was dissolved in a mixture of water (100 ml.) and ethanol (200 ml.). Potassium permanganate (5.5 gm.), dissolved in water (1100 ml.), was added in one portion with stirring, the temperature being maintained below 15°C. After three minutes the manganese dioxide was removed by filtration and the aqueous solution concentrated to a volume of 400 ml. This solution was extracted with benzene in a continuous liquid–liquid extractor for an extended length of time. From the resulting benzene extract the crude 3-(3′,4′,5′-trimethoxyphenyl)propanediol-1,2 was obtained by concentration. After recrystallization from benzene – petroleum ether (Skellysolve C), yield 12.2 gm. (52.6%), m.p. 83–84°C. Calc for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49%. Found: C, 59.48; H, 7.46%.

Oxidation of 3-(3′,4′,5′-Trimethoxyphenyl)propanediol-1,2

(*a*) *Using periodic acid.*—3-(3′,4′,5′-Trimethoxyphenyl)propanediol-1,2 (6.4 gm.) was dissolved in water (300 ml.). Paraperiodic acid (3.7 gm.) was dissolved in water (200 ml.) and this solution added dropwise to the former. After 30 min., lead nitrate (10%, 100 ml.) was added and the precipitate removed by filtration. The filtrate was extracted with ether (5×50 ml.) and then with benzene (50 ml.). The combined extracts were dried over anhydrous sodium sulphate and the solvents removed. Distillation (bath temperature, 160–190°C. at 0.05 mm.) of the residue yielded 3,4,5-trimethoxyphenylacetaldehyde (1.85 gm., 31.1%) as a viscous pale yellow oil which readily

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[2] *All melting points are uncorrected.*

crystallized on seeding, m.p. 39–40°C.; semicarbazone, m.p. 186–187°C., reported m.p. 188°C. (1).

(*b*) *Using lead tetraacetate.*—3-(3′,4′,5′-trimethoxyphenyl)propanediol-1,2 (5 gm.) was dissolved in dry benzene (55 ml.) and placed in a three-necked flask provided with a magnetic stirrer and condenser. Under reflux, lead tetraacetate (9.3 gm.) was added in small portions. After completion of the addition, the mixture was refluxed for 10 min. After cooling, the mixture was filtered, the benzene washed with water, dried, and removed by distillation. The residue was distilled (bath temperature, 160–190°C. at 0.05 mm.) to yield 3,4,5-trimethoxyphenylacetaldehyde (2.2 gm., 50.9%) as a viscous pale yellow oil which crystallized on seeding, m.p. 39–40°C.; semicarbazone, m.p. 186–188°C.

Method 2

Darzens Glycidic Ester Condensation (*2*)

From 3,4,5-trimethoxybenzaldehyde (14.8 gm.), prepared in a 75.6% yield by the methylation of syringaldehyde, and ethyl chloroacetate (9.0 gm.) with sodium ethoxide as a catalyst, there was obtained the white intermediate glycidic ester which, after recrystallization from water–ethanol, weighed 4.0 gm. This solid was added to a solution of hydrochloric acid (1.3 ml.) and water (6.8 ml.) in a flask fitted with a reflux condenser, and when it was gently warmed, gas was evolved and an oily layer separated. After one and one-half hours, the reaction mixture was cooled and extracted with benzene. This extract was washed with water (20 ml.), dried over anhydrous sodium sulphate, and concentrated to remove the solvent. Distillation (bath temperature, 160–190°C. at 0.05 mm.) of the residue yielded 3,4,5-trimethoxyphenylacetaldehyde (0.6 gm., 3.7%) as a clear viscous oil which readily crystallized, m.p. 39–40°C. Calc. for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71%. Found: C, 62.07; H, 6.56%. The semicarbazone melted at 187–188°C.

A mixed melting point between samples of the semicarbazones prepared from the 3,4,5-trimethoxyphenylacetaldehydes made by each method showed no depression, being at 187–188°C.

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1. Mauthner, F. Ann. 416: 253. 1917.
2. Newman, M. S. and Magerlein, B. J. Organic reactions. Vol. V. John Wiley & Sons, Inc., New York. 1949. p. 413.
3. Pearl, I. A. J. Am. Chem. Soc. 70: 1746. 1948.

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