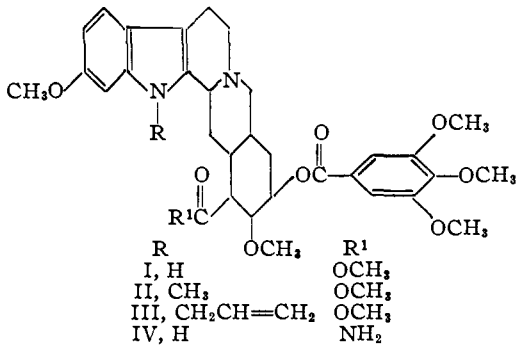
parent alkaloid. In fact, N-methylreserpine acts as a reserpine antagonist. Details of these pharmacological experiments will be published elsewhere.



| | R | $R^1$ |
|---|---|---|
| I, | H | $OCH_3$ |
| II, | $CH_3$ | $OCH_3$ |
| III, | $CH_2CH=CH_2$ | $OCH_3$ |
| IV, | H | $NH_2$ |

## Experimental[3]

**N-Methyl Methyl Reserpate.**—Methyl reserpate (2.95 g.) is added with stirring to a solution of potassium amide (prepared from 0.35 g. of potassium) in 50 ml. of liquid ammonia. Solution of methyl reserpate as the N-potassium salt occurs almost immediately. After ten minutes, a solution of 0.6 ml. of methyl iodide in 10 ml. of anhydrous ether is then added. After one-half hour of stirring, the ammonia is allowed to evaporate and the crystalline solid separating on the addition of ice-water collected. It is dissolved in hot methanol, filtered through Super-cel to remove the iron oxide used originally to catalyze the formation of potassium amide and precipitated by the addition of water. The N-methyl methyl reserpate (2.50 g.) thus obtained melts at 210–215° with a transition point at 130° probably due to loss of water of solvation. Recrystallization from ethanol gives a product melting sharply at 210–211° with no transition point.

*Anal.* Calcd. for $C_{34}H_{32}N_2O_9$: C, 67.27; H, 7.53; N, 6.54. Found: C, 67.18; H, 7.65; N, 6.71.

**N-Methylreserpine (II).**—(A) A solution of 0.4 g. of N-methyl methyl reserpate and 1.2 g. of 3,4,5-trimethoxybenzoyl chloride in 12 ml. of pyridine is allowed to stand for 4 days at room temperature and then is treated with 30 g. of ice. A precipitate of 3,4,5-trimethoxybenzoic anhydride is removed and the filtrate concentrated to dryness. The residue is dissolved in chloroform and washed successively with 2% hydrochloric acid, 2% sodium hydroxide and with water. The residue remaining after removal of the chloroform crystallizes on rubbing with methanol. This material (0.15 g.) is recrystallized by dissolving in a minimum of hot chloroform and adding methanol until needles begin to appear. N-Methylreserpine (II) melts at 265–266° and a mixture with reserpine (I) surprisingly shows no depression in melting point. Infrared absorption of N-methylreserpine in a Nujol mull shows complete absence of a band in the NH region (reserpine has a band at 3417 cm.$^{-1}$).

*Anal.* Calcd. for $C_{34}H_{42}N_2O_9$: C, 65.58; H, 6.80; N, 4.50. Found: C, 65.88; H, 6.77; N, 4.47.

(B) Finely powdered reserpine (5 g.) is added to a stirred solution of 0.35 g. of potassium in 100 ml. of anhydrous liquid ammonia. Conversion of reserpine to its potassium salt occurs relatively slowly because of the insolubility of both substances. The powdered reserpine becomes replaced by a voluminous precipitate of the potassium salt after 45 minutes of vigorous stirring. A solution of 0.5 ml. of methyl iodide in 20 ml. of anhydrous ether is added and stirring continued for 30 minutes. The ammonia is allowed to evaporate, and ice-water added with stirring gives a white powder (3.5 g.) which is collected by filtration. It is recrystallized from a large volume of acetone–water and from chloroform–methanol to give 1.8 g. of N-methylreserpine (II) indistinguishable from a sample prepared by method A.

**N-Allylreserpine (III).**—Reaction of the potassium derivative formed from 1.6 g. of methyl reserpate and the potassium amide equivalent to 0.2 g. of potassium with 0.37 ml. of allyl bromide is carried out as described above. After removal of the ammonia and addition of ice-water, an oil separates. It is extracted with chloroform and the extract washed successively with water, 2% hydrochloric acid and 2% sodium hydroxide. Removal of the chloroform (after drying over anhydrous sodium sulfate) gives 1.5 g. of crude N-allyl methyl reserpate as a gum. The latter is esterified with 3,4,5-trimethoxybenzoyl chloride and worked up as described above. The residue remaining after evaporation of the chloroform is dissolved in benzene and chromatographed on 20 g. of alumina. Development with 45 ml. of benzene elutes 1.5 g. of a yellow resinous material from the column. On trituration with methanol it crystallizes. Filtration of the crude ester and recrystallization from chloroform–methanol gives 0.5 g. of N-allylreserpine (III), m.p. 226–230°. Infrared absorption in a Nujol mull shows no band in the NH region.

*Anal.* Calcd. for $C_{36}H_{44}N_2O_9$: C, 66.65; H, 6.84; N, 4.32. Found: C, 66.67; H, 7.04; N, 4.12.

**Reserpamide.**—Finely powdered reserpine (2.5 g.) is stirred for one hour in 100 ml. of liquid ammonia with the sodium amide prepared from 2 g. of sodium. The ammonia is allowed to evaporate and 50 g. of ice-water added to the residue. The crystalline material separating is filtered. It is resuspended in 25 ml. of water and filtered again. This material (0.7 g.) is 3,4,5-trimethoxybenzamide, m.p. 178–180°. The melting point of a mixture of it with an authentic sample shows no depression. The aqueous filtrate contains the desired reserpamide. Saturation of this solution with chloroform, followed by chilling, causes the separation of 1.2 g. of crude reserpamide. It is recrystallized by the addition of ethanol to a hot aqueous solution, m.p. 270–272°.

*Anal.* Calcd. for $C_{22}H_{29}N_3O_4$: C, 66.14; H, 7.32; N, 10.52; $OCH_3$, 15.54. Found: C, 65.90; H, 7.67; N, 10.54; $OCH_3$, 15.31.

**O-3,4,5-Trimethoxybenzoylreserpamide (IV).**—Reserpamide (0.5 g.) reacts with 1.5 g. of 3,4,5-trimethoxybenzoyl chloride in 15 ml. of pyridine for three days. After most of the pyridine is removed by distillation *in vacuo*, ice and benzene are added to the residue. The solid hydrochloride of the alkaloid ester separates at the liquid interface when the mixture is shaken vigorously with an excess of 5% hydrochloric acid. The hydrochloride suspended in ethyl acetate is triturated with 5% aqueous sodium hydroxide to convert it to the base. Evaporation of the ethyl acetate solution leaves a resin which crystallizes on trituration with methanol. Recrystallization from chloroform–methanol gives 0.2 g. of O-3,4,5-trimethoxybenzoylreserpamide (IV), m.p. 240–242°.

*Anal.* Calcd. for $C_{32}H_{39}N_3O_8$: C, 64.74; H, 6.62; N, 7.08. Found: C, 64.35; H, 6.37; N, 6.99.

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(3) Melting points are uncorrected.

## Methyl 3-*O*-Methyl-α-D-glucopyranoside and Derivatives[1]

BY ROGER W. JEANLOZ AND MARCEL GUT

RECEIVED JULY 8, 1954

In the course of a study of the preparation of derivatives of 3-*O*-methyl-D-glucuronic acid, it was found necessary to prepare pure methyl 3-*O*-methyl-α-D-glucopyranoside and some of its derivatives. Reeves[2] was able to separate the mixture of α- and β-anomers obtained through glycosidification of 3-*O*-methyl-D-glucose by fractional crystallization of its 4,6-*O*-ethylidene derivative. However, the yield was very small, and the purity of the final product was uncertain. A separation of this type, using the 4,6-*O*-benzylidene derivative, was reported by Freudenberg, *et al.*,[3] but was shown by

(1) This is publication No. 167 of the Robert W. Lovett Memorial Foundation for the Study of Crippling Diseases, Harvard Medical School, Boston, Mass.

(2) R. E. Reeves, THIS JOURNAL, **66**, 845 (1944).

(3) K. Freudenberg, H. Toeppfer and C. C. Andersen, *Ber.*, **61**, 1750 (1928).

Bolliger and Prins[4] to give a crystalline mixture of the α- and β-anomers. It was therefore deemed necessary to prepare the pure α-anomer by hydrolyzing the methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-glucopyranoside which was prepared according to the method of Bolliger and Prins.[4] A sirupy product, methyl 3-*O*-methyl-α-D-glucopyranoside, which crystallized as a hydrate, was obtained. The methyl 4,6-*O*-ethylidene-3-*O*-methyl-α-D-glucopyranoside derivative of the sirup was identical with the product described by Reeves,[2] thereby demonstrating the feasibility of using such a derivative for the separation of the pure α-anomer by fractional crystallization. In addition, the following crystalline derivatives were obtained: methyl 2,4,6-tri-*O*-acetyl-3-*O*-methyl-α-D-glucopyranoside, methyl 3-*O*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside and methyl 2,4-di-*O*-acetyl-3-*O*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside.

Application of Hudson's isorotation rules to the α- and β-methylglucosides[5] of 3-*O*-methyl-D-glucose gave a difference for 2A of 38800, in agreement with the value obtained for other methylated glucosides and a sum for 2B of 28200, in agreement with the value of 26300 calculated from the rotations of the α- and β-anomers of 3-*O*-methyl-D-glucose.[6]

### Experimental[7]

**Methyl 3-*O*-Methyl-α-D-glucopyranoside.**—A solution of 6.2 g. of methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-glucopyranoside[4] in 20 ml. of methanol was heated on the water-bath with 20 ml. of 0.01 *N* sulfuric acid for two hours. After cooling, the solution was treated with barium carbonate and the filtrate was concentrated *in vacuo*. The residual sirup was distilled at 120° under a pressure of 0.001 mm. to give 4.05 g. (95%) of a pale yellow sirup. *Anal.* Calcd. for $C_8H_{16}O_6$: C, 46.15; H, 7.75; $OCH_3$, 29.81. Found: C, 46.20; H, 7.78; $OCH_3$, 29.74.

After standing in contact with the atmosphere, the sirup crystallized. Recrystallization from cold ethyl acetate gave 3.90 g. of large prisms, m.p. 80–81°, corresponding to a hemihydrate. *Anal.* Calcd. for $C_8H_{16}O_6 \cdot {}^1/_2H_2O$: C, 44.23; H, 7.89; $H_2O$, 4.15. Found: C, 44.36; H, 7.50; $H_2O$, 4.17. The rotation was calculated for the anhydrous product, $[\alpha]^{21}D$ +164 ± 2° (in water, *c* 0.86).

**Methyl 2,4,6-Tri-*O*-acetyl-3-*O*-methyl-α-D-glucopyranoside.**—Sixty milligrams of crystalline methyl 3-*O*-methyl-α-D-glucopyranoside was dried and treated with 2 ml. of anhydrous pyridine and 1 ml. of acetic anhydride overnight at room temperature. The mixture was heated at 50° for one hour, cooled and poured on ice. After extracting with chloroform, then washing with dilute sulfuric acid, sodium bicarbonate and water, the chloroform extract was dried over sodium sulfate and evaporated to dryness *in vacuo*. The residual sirup distilled at 120° under a pressure of 0.5 mm. to give a crystalline product. Recrystallization from a mixture of ether and petroleum ether gave 65 mg. (70%) of crystals, m.p. 71–72°, $[\alpha]^{21}D$ +113 ± 2° (in chloroform, *c* 1.86). *Anal.* Calcd. for $C_{14}H_{22}O_9$: C, 50.29; H, 6.63; $OCH_3$, 18.57. Found: C, 50.20; H, 6.64; $OCH_3$, 18.68.

**Methyl 4,6-*O*-Ethylidene-3-*O*-methyl-α-D-glucopyranoside.**—To a solution of 0.01 ml. of concentrated sulfuric acid in 3 ml. of paraldehyde was added 70 mg. of dry methyl 3-*O*-methyl-α-D-glucopyranoside. The mixture was shaken for two days, then water and petroleum ether were added. After shaking well, the aqueous layer was separated, and extracted twice with petroleum ether. The aqueous layer was then extracted with chloroform 4 times and the chloroform extracts were evaporated *in vacuo* to give 65 mg. (82%) of crystalline residue. It was dissolved in a mixture of benzene and hexane and chromatographed on alumina. Elution with mixtures of benzene and hexane gave crystalline fractions, which after recrystallization from a mixture of ether and petroleum ether melted at 106–107°, $[\alpha]^{21}D$ +150 ± 5° (in chloroform, *c* 0.46); $[\alpha]^{24}D$ +119 ± 5°, $[\alpha]^{24}_{4361}$ +240 ± 5° (in water, *c* 0.5).[8]

**Methyl 3-*O*-Methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside.**—To a solution of 0.57 g. of dry methyl 3-*O*-methyl-α-D-glucopyranoside in 4 ml. of anhydrous pyridine was added 0.9 g. of triphenylchloromethane. The solution was heated at 100° for two hours. After cooling, the solution was treated with a small amount of ice, extracted with chloroform and the extracts washed with ice-cold dilute hydrochloric acid, dilute sodium carbonate and water and dried over sodium sulfate. Evaporation of the solvent *in vacuo* left 1.5 g. of a yellow sirup, which was crystallized from benzene. Repeated recrystallizations gave 510 mg. (43%) of large prisms, m.p. 115–118°, $[\alpha]^{25}D$ +64 ± 2° (in chloroform, *c* 1.73). *Anal.* Calcd. for $C_{27}H_{30}O_6$: C, 71.98; H, 6.71. Found: C, 71.82; H, 6.68.

**Methyl 2,4-Di-*O*-acetyl-3-*O*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside.**—A solution of 2.25 g. of dry methyl 3-*O*-methyl-α-D-glucopyranoside was heated with 3.44 g. of triphenylchloromethane and 16 ml. of dry pyridine as described above; 32 ml. of dry pyridine and 15 ml. of acetic anhydride were then added and the solution left standing at room temperature for 24 hours. It was poured on ice and after 3 hours extracted with chloroform as described above. The sirup was dissolved in a mixture of benzene and hexane and chromatographed on alumina. Elution with mixtures of benzene and hexane gave crystalline fractions, which after recrystallization from methanol afforded 4.1 g. (70%) of prisms, m.p. 159–161°, $[\alpha]^{25}D$ +84 ± 2° (in chloroform, *c* 1.59). *Anal.* Calcd. for $C_{31}H_{34}O_8$: C, 69.95; H, 6.41. Found: C, 69.58; H, 6.46.

Acetylation of methyl 3-*O*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside gave a product identical by m.p. and mixed m.p. with the product described above.

(4) H. R. Bolliger and D. A. Prins, *Helv. Chim. Acta*, **28**, 465 (1945).

(5) B. Helferich and O. Lang, *J. prakt. Chem.*, **132**, 321 (1932).

(6) J. C. Irvine and J. P. Scott, *J. Chem. Soc.*, **103**, 564 (1913); J. C. Irvine and T. P. Hog, *ibid.*, **105**, 1386 (1914); C. G. Anderson, W. Charlton and W. N. Haworth, *ibid.*, 1329 (1929).

(7) R. W. Jeanloz, THIS JOURNAL, **76**, 555 (1954).

(8) Reeves[2] reported m.p. 106–107°, $[\alpha]^{25}D$ +114°, $[\alpha]^{25}_{4361}$ +246° (in water, *c* 0.6).

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## 1,1-Diphenyl-1-(β-diethylaminoethoxy)-2-butanone

BY PAULA KAUFMANN,[1] MILTON B. FRANKEL[2] AND HARRY S. MOSHER

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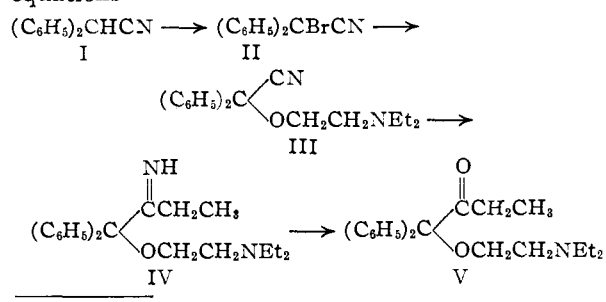
In the preparation of several diphenylmethane derivatives[3] difficulties were encountered in the preparation of 1,1-diphenyl-1-(β-diethylaminoethoxy)-2-butanone (V) by the steps indicated in the equations

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(2) Parke, Davis and Co. Research Fellow, 1947–1949.

(3) H. S. Mosher, M. B. Frankel and M. Gregory, THIS JOURNAL, **75**, 5326 (1953).