[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Methyl Glucoside Carbanilates. III. Methyl β-D-Glucoside-2,3,6-tricarbanilate[1]

BY W. M. HEARON[2] AND ROBERT S. BARNES, JR.

Carbanilates of carbohydrates are finding increasing use[3,4,5,6] because of their ease of formation and excellent properties as derivatives. To those already reported, we now add methyl β-D-glucoside-2,3,6-tricarbanilate, which, with the corresponding alpha compound,[3a] is of interest as a possible breakdown product of carbanilated cellulose,[7] and starch.

The preparation of this compound has been carried out, as in the alpha series, by the sequence of reactions

Methyl β-D-glucoside-2,3-dicarbanilate (I)
↓
Methyl 6-trityl-β-D-glucoside-2,3-dicarbanilate (II)
↓
Methyl 6-trityl-β-D-glucoside-2,3-dicarbanilate-4-acetate (III)
↓
Methyl β-D-glucoside-2,3-dicarbanilate-4-acetate (IV)
↓
Methyl β-D-glucoside-2,3,6-tricarbanilate-4-acetate (V)
↓
Methyl β-D-glucoside-2,3,6-tricarbanilate (VI)

As with methyl D-glucosides,[8] tritylation and acetylation of methyl β-D-glucoside-2,3-dicarbanilate could be carried out without isolation of the intermediate and in better yield than stepwise. The tricarbanilate formed, possessed a melting point and optical rotation differing from those of the corresponding alpha derivative and from those of the two methyl D-glucoside-2,3,4-tricarbanilates, but gave on further carbanilation the tetrasubstituted derivative previously prepared.[9]

Experimental

Methyl 6-Trityl-β-D-glucoside-2,3-dicarbanilate (II).—A solution of 1.9 g. of methyl β-D-glucoside-2,3-dicarbanilate[3a] and 1.22 g. of trityl chloride in 5 ml. of dry pyridine was heated in a stoppered flask on a steam-bath for one hour. After cooling, the solution was diluted with 20 ml. of ordinary pyridine and poured into cold water. The white precipitate was collected and recrystallized from hot methanol giving 1.88 g. or 60% yield melting at 114–115°; $\alpha^{25}D$ −17° (acetone, $C = 1$).

Anal. Calcd. for $C_{40}H_{38}O_8N_2$: CH_3O, 4.60; trityl, 36.1. Found: CH_3O, 4.67; trityl, 35.9.

Methyl 6-Trityl-β-D-glucoside-2,3-bicarbanilate-4-acetate (III). A. By Acetylation of Methyl 6-Trityl-β-D-glucoside-2,3-dicarbanilate.—A solution of 1.0 g. methyl 6-trityl-β-D-glucoside-2,3-dicarbanilate in 5 ml. of dry pyridine and 2 g. of acetic anhydride was left sixteen hours at room temperature. Pouring the solution into cold water gave a precipitate which crystallized from hot ethanol–ethyl acetate and amounted to 0.85 g. or 88% yield, melting at 202–204°; $\alpha^{25}D$ −3° (ethyl acetate, $C = 1$).

Anal. Calcd. for $C_{42}H_{40}O_9N_2$: C, 70.4; H, 5.58; N, 3.91. Found: C, 69.7; H, 5.77; N, 4.02.

B. By Tritylation and Acetylation of Methyl β-D-Glucoside-2,3-dicarbanilate.—A solution of 2.4 g. of methyl β-D-glucoside-2,3-dicarbanilate in 5 ml. of dry pyridine with 1.5 g. of trityl chloride was heated on a steam-bath for one hour. After cooling, 2.5 ml. of acetic anhydride was added and the solution left at room temperature for sixteen hours. It was then diluted with 10 ml. of ordinary pyridine and poured into 400 ml. of cold water. The precipitate formed was collected and crystallized from hot ethanol–ethyl acetate giving 3.4 g. or 89.5% yield melting at 202–204°; mixed m. p. with product from A above, 202–204°.

Methyl β-D-Glucoside-2,3-dicarbanilate-4-acetate (IV).—A cold solution of 3.0 g. of methyl 6-trityl-β-D-glucoside-2,3-dicarbanilate-4-acetate in 10 ml. of glacial acetic acid was treated with 10 ml. of hydrobromic acid in acetic acid (made by adding 11 ml. of 42% hydrobromic acid carefully to 46 ml. of cold acetic anhydride). After two minutes, the solution was filtered and run immediately into 200 ml. of cold water. The precipitate was collected, washed with hot ligroin, and crystallized from hot water giving 1.2 g. or 60% yield melting at 151–152°, $\alpha^{25}D$ −21° (acetone, $C = 1$).

Anal. Calcd. for $C_{23}H_{26}O_9N_2$: C, 58.2; H, 5.48; N, 5.90. Found: C, 59.0; H, 5.40; N, 5.97.

Methyl β-D-Glucoside-2,3,6-tricarbanilate-4-acetate (V).—A solution of 2.0 g. of methyl β-D-glucoside-2,3-dicarbanilate-4-acetate in 5 ml. of dry pyridine with 0.8 g. of phenyl isocyanate (1.4 times theory) was heated on a steam-bath for one hour. After cooling, the solution was diluted with 2 ml. of methanol and allowed to stand for ten minutes. Ten ml. of ordinary pyridine was then added and the solution poured into 200 ml. of cold water. The precipitate was collected, washed with hot ligroin and crystallized from hot methanol giving 1.5 g. or 60% yield, melting at 173–174°; $\alpha^{25}D$ −3° (acetone, $C = 1$).

Anal. Calcd. for $C_{30}H_{31}O_{10}N_3$: C, 60.7; H, 5.22; N, 7.08. Found: C, 61.0; H, 5.40; N, 6.90.

Methyl β-D-Glucoside-2,3,6-tricarbanilate (VI).—A solution of 1.0 g. of methyl β-D-glucoside-2,3,6-tricarbanilate-4-acetate in 20 ml. of methanol containing 0.5% hydrogen chloride was refluxed for two hours. After cooling, the hydrogen chloride was removed with barium carbonate and the solution evaporated to dryness by an air stream. The residue was crystallized from petroleum ether–acetone giving 0.5 g. or 54% yield melting at 197–198°; $\alpha^{25}D$ −15 (acetone, $C = 1$).

Anal. Calcd. for $C_{28}H_{29}O_9N_3$: C, 61.0; H, 5.27; N, 7.62. Found: C, 60.7; H, 5.21; N, 7.49.

Methyl β-D-Glucoside-2,3,4-tricarbanilate-6-acetate.—Acetylation of 0.9 g. of methyl β-D-glucoside-2,3,4-tricarbanilate in 6 ml. of dry pyridine with 3 ml. of acetic anhydride on the steam-bath for one hour gave 1.0 g. of crude (100%) and 0.8 g. of pure (82%) white crystals from ethanol melting at 229–230°; $\alpha^{25}D$ +5° (acetone, $C = 1$). A mixture of this product and its precursor melted at 218–219°.

(1) Presented before the Division of Sugar Chemistry at the 116th meeting of the American Chemical Society, Atlantic City, New Jersey.

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(3) (a) *Cf.* Hearon, Hiatt and Fordyce, THIS JOURNAL, **66**, 995 (1944); (b) Hearon, *ibid.*, **70**, 297 (1948).

(4) Reeves, *ibid.*, **70**, 259 (1948).

(5) (a) Wolff and Rist, *ibid.*, **70**, 2779 (1948); (b) Wolff and Rist, *ibid.*, **70**, 3961 (1948).

(6) Reeves and Jung, *ibid.*, **71**, 215 (1949).

(7) Hearon, Hiatt and Fordyce, *ibid.*, **65**, 829 (1943).

(8) Helferich, Klein and Snyder, *Ber.*, **59**, 81 (1926).

(9) Wolfrom and Pletcher, THIS JOURNAL, **62**, 1151 (1940).

Anal. Calcd. for $C_{30}H_{31}O_{10}N_3$: CH_3O, 5.22; acetyl, 7.25. Found: CH_3O, 5.02; acetyl, 7.22.

Methyl β-D-Glucoside-2,3,4,6-tetracarbanilate.—A small amount of methyl β-D-glucoside-2,3,6-tricarbanilate was carbanilated in dry pyridine with phenyl isocyanate giving, from hot acetone, white crystals melting at 221–222°. This product did not depress the melting point of the methyl β-D-glucoside-2,3,4,6-tetracarbanilate made by direct carbanilation of methyl β-D-glucoside.[9]

Summary

1. Crystalline methyl β-D-glucoside-2,3,6-tricarbanilate has been prepared from methyl β-D-glucoside-2,3-dicarbanilate in a five-step synthesis.

2. The intermediates in this synthesis, all crystalline, have been described and identified.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Steroid Analogs Lacking Ring C. II. Some Analogs of Progesterone and Desoxycorticosterone

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In seeking synthetic compounds which might show the hormonal activity of testosterone, progesterone or desoxycorticosterone, it has seemed attractive to us to prepare analogs of the hormones lacking Ring C. In the present paper is described the synthesis of such analogs of progesterone and desoxycorticosterone. In these initial approaches, begun in 1941 and interrupted during the war, we have aimed the synthesis for reasons of simplification toward structures of the type of XIV and XV lacking the angular methyl groups and with a six-membered ring D, with the intention of extending the work to closer analogs should the physiological tests be encouraging.

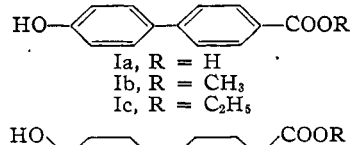
For the synthesis of these α,β-unsaturated cyclic ketones we have employed the very useful Robinson–Mannich base method[3] with the perhydrogenated biphenyl keto acid IVa. Recently we have described an improved modification of this method using the 2-hydroxymethylene derivative of 4-cyclohexylcyclohexanone to synthesize 6-cyclohexyl-Δ^{1-9}-octalone-2 (XIV, R = H).[4]

The intermediate keto acid IVa was prepared from 4-(4′-hydroxyphenyl)-benzoic acid (Ia), which is readily available from 4-methoxybiphenyl.[5,6] Hydrogenation of the methyl ester of the hydroxy acid in the presence of W-6 Raney nickel catalyst gave a mixture of isomeric perhydro hydroxy esters IIb from which only one of the four stereoisomers could be isolated in pure form. Oxidation of the mixture of hydroxy acids, however, gave the two possible keto acids IVa, from which were obtained Isomer A, m. p. 174–175° (22% over-all yield from Ib) and Isomer B, m. p. 96–96.5° (36% over-all yield).

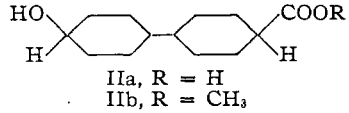
It was also possible to limit the hydrogenation of the ester Ic so as to obtain material (IIIc) with only one ring reduced. After oxidation of the non-phenolic fraction, the keto acid VIIIa was obtained in 45–48% yield, along with some of the fully reduced acid IVa. None of the phenolic acid was isolated with the carboxyl-substituted ring reduced, which is the product of sodium and alcohol reduction of Ia.[6]

The conversion of the keto esters IVb (Isomer A) and VIIIb to the tricyclic unsaturated keto acids VIIa and XIa followed the procedure applied by us to 4-cyclohexylcyclohexanone in preparing the simpler ketone XIV (R = H).[4] In the condensation of the keto esters with methyl formate, very satisfactory yields (91–86% of the hydroxymethylene derivatives Va and IXa resulted when an excess of the reagents was used.[7] It is worthy of note that the esters Vb and IXb, the primary reaction products, were saponified in excellent yields under very mild conditions in working up the reaction mixtures.

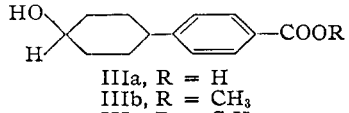
Either the hydroxymethylene acids or esters were suitable for the Mannich base condensation, in the former cases an additional equivalent of sodium methoxide being used to prepare the salts. In this reaction the crystalline products were largely VIa (or VIc) and Xa (or Xc), in which the formyl group was eliminated. Cy-



Ia, R = H
Ib, R = CH_3
Ic, R = C_2H_5



IIa, R = H
IIb, R = CH_3



IIIa, R = H
IIIb, R = CH_3
IIIc, R = C_2H_5

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(3) See du Feu, McQuillin and Robinson, *J. Chem. Soc.*, 53 (1937), and later papers.

(4) Shunk and Wilds, THIS JOURNAL, **71**, 3946 (1949).

(5) Fieser and Bradsher, *ibid.*, **58**, 1738 (1936).

(6) Johnson, Gutsche and Offenhauer, *ibid.*, **68**, 1648 (1946).

(7) There was no indication of the formation of bis-hydroxymethylene derivatives; the ultraviolet absorption spectrum showed a single maximum at 281 mμ with no indication of a maximum at around 300–310 mμ as would be expected for a bis-hydroxymethylene derivative.