180° during 15 min. After cooling to room temperature, the product was taken up in water and washed with chloroform. The aqueous solution was saturated with carbon dioxide and again extracted with chloroform. Upon evaporation of the solvent an oily mass remained which was submitted to vacuum sublimation at 120°, 0.005 mm. Two resublimations yielded colorless crystals of antiarol (IIIb) (5 mg.), m.p. 144–146° (lit.[3] m.p. 145.5–146°). Identity with an authentic sample was established by mixture melting point determination and by infrared spectral comparison; λ_{max} (in Nujol mull) 3.03, 6.16, 12.16, and 12.84 μ.

The degradation product IIIb was treated with boiling acetic anhydride and anhydrous sodium acetate. Crystallization from ethanol afforded colorless prisms of *O*-acetylantiarol, m.p. 73–74° (lit.[19] 74°).

The above aqueous solution was now acidified with dilute hydrochloric acid and extracted with ether. Evaporation of the solvent afforded a crystalline mass which was purified by three vacuum sublimations to yield colorless crystals of homoasaronic acid (IV), melting partially at 78°, resolidifying and melting finally at 84–87° (lit.[16] m.p. 87°). Identity of this product was established as outlined above.

Asaronic acid. A solution of caviunin (Ia) (90 mg.) in 5 ml. of 3% aqueous sodium hydroxide was treated at 50° with small portions of potassium permanganate solution until the consumption of the oxidant subsided. The excess permanganate was reduced with sodium sulfite, the precipitate separated by filtration and washed with 3% sodium hydroxide solution. The combined filtrates were acidified and extracted with chloroform. The organic layer was washed with concentrated sodium bicarbonate solution. This yielded, after acidification and extraction with chloroform, 40 mg. of a slightly yellow solid which was washed with a little ethanol. Vacuum sublimation afforded white crystals of asaronic acid, m.p. 144–145° (lit.[16] m.p. 144–145.5°). Identity with an authentic sample of 2,4,5-trimethoxybenzoic acid was established by mixture melting point determination and infrared spectral comparison; λ_{max} (in Nujol mull), *inter al.*, 5.80, 6.00, 7.77, 8.23, 9.26, and 9.80 μ. Nitration yielded 1-nitro-2,4,5-trimethoxybenzene,[16] m.p. and mixture m.p. with an authentic sample 128–130°.

Oxidation of caviunin (Ia) with alkaline hydrogen peroxide[20] also yielded asaronic acid.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLLEGE OF SCIENCE AND TECHNOLOGY, BRISTOL, AND THE DEPARTMENT OF ORGANIC CHEMISTRY, UNIVERSITY OF BRISTOL]

Synthesis of Isoflavones. Part III.[1] Caviunin

S. F. DYKE, W. D. OLLIS, AND M. SAINSBURY

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The synthesis of caviunin (5,7-dihydroxy-2′,4′,5′,6-tetramethoxyisoflavone) using the ethoxalylation method is described.

At the suggestion of Dr. Gottlieb and Dr. Magalhães, whose interest we are pleased to acknowledge, we have investigated the synthesis of caviunin whose determination of structure is described in the preceding paper.[2] Of the various methods which are available for the synthesis of isoflavones,[3] the method due to Baker and Ollis[4] involving the reaction of benzyl *o*-hydroxyphenyl ketones with ethoxalyl chloride is particularly suitable for the synthesis of isoflavones bearing several hydroxyl groups.

Caviunin is one of the more unusual types of isoflavone in that it is a derivative of 5,7-dihydroxy-6-methoxyisoflavone. This class includes tectorigenin (I), irigenin (II), and podospicatin[5] (III) as well as caviunin (IV). Previously the synthesis of isoflavones in this class has presented some difficulty but recently it was shown that the ethoxalylation method could be used for the synthesis of tectorigenin and irigenin.[6] By a similar method, the followed synthesis of caviunin has been achieved.

Hoesch condensation of iretol and 2,4,5-trimethoxybenzyl cyanide yielded the benzyl *o*-hydroxyphenyl ketone (VII). This ketone was treated with ethoxalyl chloride in pyridine solu-

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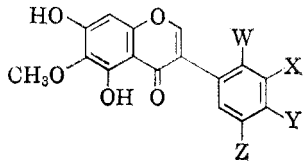
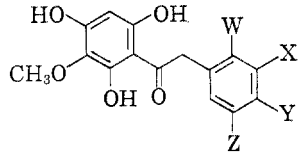
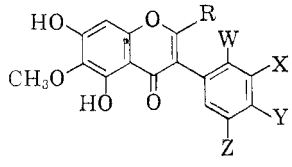


I. W = H; X = H; Y = OH; Z = H
II. W = H; X = OH; Y = OCH_3, Z = OCH_3
III. W = OH; X = H; Y = H; Z = OCH_3
IV. W = OCH_3; X = H; Y = OCH_3; Z = OCH_3

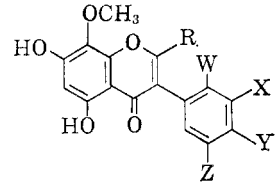


V. W = H; X = H; Y = OH; Z = H
VI. W = H; X = OH; Y = OCH_3; Z = OCH_3
VII. W = OCH_3; X = H; Y = OCH_3; Z = OCH_3

tion and the total ethoxalylation product was hydrolyzed with alkali and thermally decarboxylated. The decarboxylation reaction product was purified by chromatography on thick paper and yielded the isoflavone (IV) which was identical with caviunin. The synthetic isoflavone was characterized as its diacetate and both these compounds gave very detailed infrared spectra which were identical with the infrared spectra of caviunin and its diacetate.



VIII



IX

It was expected from our experiences with the synthesis of tectorigenin and irigenin[6] that this synthesis would have yielded both caviunin (VIII. R = X = H; W = Y = Z = OCH_3) and its isomer (IX. R = X = H; W = Y = Z = OCH_3). However, chromatographic examination of the total ethoxalylation product from the ketone (VII) did not indicate that it was a mixture of the two possible products (VIII and IX. R = $CO_2C_2H_5$; X = H; W = Y = Z = OCH_3). Furthermore, the isomer (IX. R = X = H; W = Y = Z = OCH_3) of caviunin was not present in detectable amounts in the total product obtained by hydrolysis and decarboxylation of the crude 2-carbethoxyisoflavone. This result certainly contrasts with our earlier experiences in synthetical approaches to tectorigenin (I) and irigenin (II), when the 2-carbethoxy-Ψ-tectorigenin (IX. R = $CO_2C_2H_5$; W = X = Z = H; Y = OH) and 2-carbethoxy-Ψ-irigenin (IX. R = $CO_2C_2H_5$; W = H; X = OH; Y = Z = OCH_3) were the compounds which were more easily isolated from the mixture produced in the ethoxalylation reaction. Clearly the relative proportions of the two possible products (see VIII and IX. R = $CO_2C_2H_5$) which could be formed from a ketone of the type derived from iretol (see V–VII) are controlled by subtle features.

EXPERIMENTAL

2,4,5-Trimethoxybenzyl 2,4,6-trihydroxy-3-methoxyphenyl ketone (VII). A mixture of iretol[7] (4.2 g.), 2,4,5-trimethoxybenzyl cyanide[8] (6.0 g.) and anhydrous zinc chloride (5.0 g.) in anhydrous ether (150 ml.) was saturated with dried hydrogen chloride during 5 hr. at 0° and after keeping at 0° for 1 week, the ether solution was decanted from the oily layer of ketimine hydrochloride–zinc chloride complex which had separated. The oily layer was shaken twice with dry ether (250 ml.) then heated (nitrogen atmosphere) on a steam bath with water (400 ml.) which had been previously boiled with a stream of nitrogen bubbling through it. After cooling and standing, the product was collected and recrystallized from aqueous ethanol giving the ketone (VII) (5.9 g., 60%) as almost colorless rhombs, m.p. 211–212°. The ultraviolet spectrum in 95% ethanol showed a maximum at 291 mμ (log ε 3.39), an inflection at 340 mμ (log ε 2.54) and a minimum at 253 mμ (log ε 2.13).

Anal. Calcd. for $C_{18}H_{20}O_8$: C, 59.46; H, 5.50. Found: C, 59.45; H, 5.79.

Caviunin (IV). The above ketone (VII) (2.48 g.) was dissolved in dry pyridine (50 ml.) and ethoxalyl chloride (4.5 ml.) added with shaking at 0°. After keeping at 0° for 3 days, it was poured into water and extracted with chloroform. The extract was washed with dilute sulfuric acid and with water, dried (magnesium sulfate), and evaporated to yield the 2-carbethoxyisoflavone (3.18 g.) as an oil which showed one main spot (R_f = 0.86) by chromatography[9] on Whatman No. 3 paper.

This oil (3.10 g.) was dissolved in acetone (150 ml.) and added to a mixture of air free water (750 ml.) and 2*N* aqueous sodium hydroxide (33 ml.). After keeping at room temperature for 12 hr., acidification and extraction with chloroform yielded the isoflavone-2-carboxylic acid as a light brown amorphous solid (2.9 g.). Chromatography[9] on Whatman No. 1 paper gave one main spot (R_f 0.79) when examined under ultraviolet light.

A portion (860 mg.) of this crude isoflavone-2-carboxylic acid was divided into 40 small portions (*ca.* 20 mg.). Each small portion was placed in an ignition tube and heated at 295° for 3–3.5 min., when decarboxylation was completed. The product was removed from the ignition tubes with warm ethanol giving a gum (649 mg.) which was chromatographed on silica and eluted with chloroform. The chloroform eluate (438 mg.) was chromatographed[9] on Whatman (No. 3 MM) thick paper and the strip bearing the major band (R_f = 0.75–0.90) was cut out and eluted with ethanol yielding a crystalline compound (222 mg.). This material showed R_f %. Asin 0.72 identical with that of caviunin on paper chromatography.[9] Recrystallization of this fraction from chloroform and from ethanol gave caviunin as colorless needles, m.p. and mixed m.p. 191–192°.

Anal. Calcd. for $C_{15}H_6O_4$ $(OCH_3)_4$: C, 60.96; H, 4.85; OCH_3, 33.16. Found: C, 60.46; H, 5.48; OCH_3, 32.67.

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The synthetic caviunin was characterized as its diacetate, colorless crystals from ethanol, m.p. and mixed m.p. 197.5°.

Anal. Calcd. for $C_{19}H_{16}O_6$ $(OCH_3)_4$; C, 60.26; H, 4.84; OCH_3, 27.1. Found: C, 59.91; H, 5.18; OCH_3, 28.7.

The natural and synthetic caviunin gave identical infrared (Nujol mull) and ultraviolet spectra. The infrared spectra (Nujol mull) of the diacetates were also identical.

BRISTOL 8, ENGLAND

[CONTRIBUTION FROM THE ARTHRITIS RESEARCH LABORATORY, DEPARTMENTS OF MEDICINE AND BIOCHEMISTRY, UNIVERSITY OF ALABAMA MEDICAL CENTER]

Methyl Derivatives of D-Mannosamine

WOLFGANG ROTH AND WARD PIGMAN

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By replacement of a *p*-tolylsulfonyloxy group with hydrazine and subsequent reductions, 2-amino-2-deoxy-3-*O*-methyl-D-mannose hydrochloride and crystalline 2-amino-2-deoxy-3,5,6-tri-*O*-methyl-D-mannose hydrochloride and their crystalline methyl β-glycosides were prepared. Other new amorphous intermediates are reported.

The interest in the preparation of methylated derivatives of 2-amino-2-deoxy-D-mannose arises from the finding of D-mannosamine as a structural entity of the biochemically important neuraminic acid.[1] The methods for the preparation of 2-amino-2-deoxy-D-mannose[2–6] require the separation of this sugar from its epimeric isomer in one step of the procedure. We are reporting the preparation of methyl ethers of D-mannosamine by a method which avoids such a separation and leads unambiguously only to compounds with a 2-amino-2-deoxy-D-mannose configuration.

It has been shown that the replacement of a *p*-tolylsulfonyloxy group with hydrazine[7] in appropriately substituted sugars proceeds with Walden inversion.[8–10] The application of this reaction to 2-*O*-*p*-tolysulfonyl-D-glucose derivatives should therefore yield compounds with a 2-hydrazino-2-deoxy-D-mannose configuration in which the hydrazino group should be reducible to an amino group.[8,11]

In an effort to get the unsubstituted D-mannosamine, we prepared the methyl 2-*O*-*p*-tolylsulfonyl-3,5,6-tri-*O*-benzyl-α,β-D-glucofuranoside by tosylation of methyl 3,5,6-tri-*O*-benzyl-α,β-D-glucofuranoside[12] in pyridine. The replacement of the *p*-tolylsulfonyloxy group with hydrazine, however, was not achieved even after a prolonged period of refluxing (four days). The steric effect of a large benzyl group in the 3- position or even in the 5- and 6- positions seems the probable basis for this lack of reactivity.

In order to test this supposition, the reaction was then carried out on the corresponding 3-*O*-methyl-5,6-di-*O*-benzyl derivative. This compound was prepared by benzylation of 1,2-*O*-isopropylidene-3-*O*-methyl-D-glucofuranose (I)[14] with benzyl chloride and potassium hydroxide, yielding 1,2-*O*-isopropylidene-3-*O*-methyl-5,6-di-*O*-benzyl-D-glucofuranose (II). With methanolic hydrogen chloride the isopropylidene group was split off, and a mixture of the α- and β-glycosides (III) was formed. Tosylation of III in pyridine yielded methyl 2-*O*-*p*-tolylsulfonyl-3-*O*-methyl-5,6-di-*O*-benzyl-α,β-D-glucofuranoside (XV). For this compound, also, a replacement of the *p*-tolysulfonyloxy group with hydrazine could not be achieved.

To show whether benzyl groups in the 5- or 6-positions would prevent a back-side displacement by hydrazine of the *p*-tolylsulfonyloxy group, the methyl 2-*O*-*p*-tolylsulfonyl-3,5,6-tri-*O*-methyl-β-D-glucofuranoside was prepared by tosylation of the known methyl 3,5,6-tri-*O*-methyl-β-D-glucofuranoside.[13] This compound was found to react with hydrazine. On subsequent hydrogenation with Raney nickel catalyst the methyl 2-amino-2-deoxy-3,5,6-tri-*O*-methyl-β-D-mannofuranoside was isolated as a crystalline hydrochloride. Hydrolysis with hydrochloric acid yielded the crystalline 2-amino-2-deoxy-3,5,6-tri-*O*-methyl-D-mannose hydrochloride.

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