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The Pictet–Spengler Reaction in Carbohydrate Chemistry. Reactions of Sugars with Biogenic Amines

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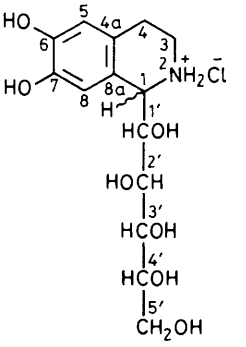
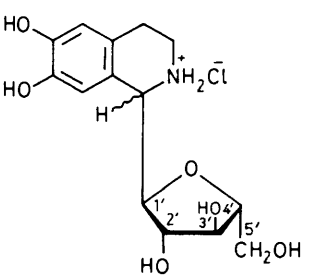
Pictet–Spengler condensations of dopamine with D-glucose and 2,5-anhydro-D-mannose, and of tryptamine with 2,5-anhydro-D-mannose, have afforded novel tetrahydroisoquinolines and a β-carboline respectively.

The reactions between amines and sugars, both *in vitro* and *in vivo*, are of several types and of profound significance.[1] Amongst these are the well known Maillard reaction that is believed to proceed by formation of a glycosylamine that is further transformed by the Amadori rearrangement.[2] The present research is concerned with the investigation of the reaction of biogenic amines with sugars by way of a Pictet–Spengler condensation, a reaction which to our knowledge has not been seriously studied.[3] The resulting products are novel tetrahydroisoquinolines and β-carbolines, compounds of value as synthons in enantioselective synthesis of alkaloids and other natural products; moreover, the products can also be viewed as a novel class of *C*-nucleosides.

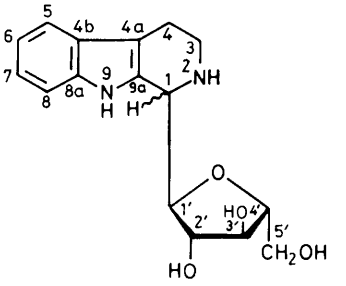
A solution of dopamine [2-(3,4-dihydroxyphenyl)ethylamine] hydrochloride and D-glucose in water was heated at reflux temperature for 48 h; the mixture was filtered, the filtrate was treated with ion-exchange resin (H^+ form), and the product was purified by chromatography on silica gel using 9:1 (v/v) acetonitrile–water as eluant, to afford a mixture of diastereoisomers (**1**) as a yellow-brown powder in 92% yield. The ^{13}C n.m.r. and ^1H n.m.r. data are consistent with the proposed structure and indicate that the diastereoisomeric ratio is *ca.* 4:1. The ^{13}C n.m.r. assignments for the tetrahydroisoquinoline moiety were made in analogy with reported[4] spectra of 1-substituted tetrahydroisoquinolines; ^{13}C n.m.r. (50.3 MHz; D_2O):†‡ δ 24.7, 25.6 (C-4), 40.4, 42.1 (C-3), 57.9, 59.9 (C-1), 63.6 (C-5′), 70.5, 69.9 (C-1′), 72.3 and 73.4 (C-2′, -3′, -4′), 115.3, 114.5 (C-8), 117.0 (C-5), 121.7, 120.8 (C-8a), 126.4 (C-4a), 144.0 (C-7), and 145.3 p.p.m. (C-6); ^1H n.m.r. (200 MHz; D_2O):‡§ δ 2.88—3.12 (2H, m, H's at C-4),



(1)



(2)



(3)

† All ^{13}C chemical-shift data are in p.p.m. from $SiMe_4$; 1,4-dioxan (δ 67.45 p.p.m.) was used as the internal reference.

‡ In those cases in which two values are given, the first value refers to the chemical shift of a signal for the major isomer.

§ For all the ^1H n.m.r. spectra, sodium 4,4-dimethyl-4-silapentane-1-sulphonate was employed as the internal standard.

3.60—3.93 (6H, m, H's at C-3, C-3′, C-4′, and C-5′), 4.16 (1H, t, *J* 2 Hz, H at C-2′), 4.37 (1H, dd, $J_{1',2'}$ 2 Hz, $J_{1',1}$ 4.5 Hz, H at C-1′), 4.71, 4.61 (2 × d, $J_{1,1'}$ 4.5 Hz, H at C-1 for each isomer), 6.80, 6.77, and 6.87, 6.84 (each s, H's at C-5 and C-8 for each isomer).

2,5-Anhydro-D-mannose[5] was prepared by treatment of an aqueous solution of 2-amino-2-deoxy-D-glucopyranose hydrochloride with sodium nitrite and ion-exchange resin (H^+ form). The solution was neutralized using an ion-exchange resin (OH^- form), and dopamine hydrochloride was added. After 2 days at room temperature, a mixture of diastereoisomers (**2**) was isolated as a yellow-brown powder in 98% yield by chromatography on silica gel using 9:1 (v/v) acetonitrile–water as eluant. The ^{13}C n.m.r. spectrum indicated that the diastereoisomeric ratio was *ca.* 4:1; ^{13}C n.m.r. (50.3 MHz; D_2O):†‡ δ 24.6, 25.0 (C-4), 39.9, 41.5 (C-3), 56.5 (C-1), 62.4 (C-5′), 78.5, 77.2, and 79.2, and 83.2, 84.0, and 84.9, 85.6 (C-1′, -2′, -3′, -4′), 115.5 (C-8), 117.1 (C-5), 120.9, 120.2 (C-8a), 126.1 (C-4a), 143.9 (C-7), and 145.5 p.p.m. (C-6); ^1H n.m.r. (200 MHz; D_2O):‡§ δ 2.99—3.17 (2H, m, H's at C-4), 3.58—3.91 (4H, m, H's at C-3 and C-5′), 4.13 (1H, m, H at C-4′), 4.19 (1H, t, *J* 5 Hz, H at C-2′), 4.28 (1H, dd, $J_{1',2'}$ 5 Hz, $J_{1',1'}$ 7.5 Hz, H at C-1′), 4.41 (1H, t, *J* 5 Hz, H at C-3′), 4.71 (1H, d, $J_{1,1'}$ 7.5 Hz, H at C-1), 6.83 and 6.89 (2 × s, H's at C-5 and C-8).

A mixture of the diastereoisomeric β-carbolines (**3**) was obtained as a yellow-brown powder in 98% yield by the reaction of 2,5-anhydro-D-mannose and tryptamine hydrochloride for 7 days at room temperature. The ^{13}C n.m.r. spectrum indicated that the diastereoisomeric ratio was *ca.* 3:2; ^{13}C n.m.r. (50.3 MHz; D_2O):†‡ δ 18.7 (C-4), 41.8, 43.1 (C-3), 55.0, 55.3 (C-1), 62.1, 62.3 (C-5′), 77.7, 77.2; 78.8, 78.6; 81.4, 82.4; 84.4, 85.0 (C-1′, -2′, -3′, -4′), 108.9, 108.3 (C-4a), 112.7 (C-8), 119.3 (C-5), 120.8 (C-6), 123.9, 123.8 (C-7), 126.4, 126.5 (C-9a), 127.3 (C-4b), and 137.5 p.p.m. (C-8a); ^1H n.m.r. (200 MHz; D_2O):‡§ δ 2.87—3.18 (2H, m, H's at C-4), 3.63—4.02 (4H, m, H's at C-3 and C-5′), 4.08—4.46 (4H, m, H's at C-1′, C-2′, C-3′, and C-4′), 4.50 (1H, d, $J_{1,1'}$ 6 Hz, H at C-1), 7.25 and 7.37 (2 × t, *J* 7.5 Hz, H's at C-6 and C-7), 7.56 and 7.62 (2 × d, $J_{5,6} = J_{7,8} = 7.5$ Hz, H's at C-5 and C-8). In contrast to the cases of (**1**) and (**2**), (**3**) was obtained as a free base rather than as a hydrochloride.

Mass spectral data for several derivatives of (**1**)—(**3**) are in accord with the assigned structures and will be discussed elsewhere. A biological evaluation of the new products is in progress.

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