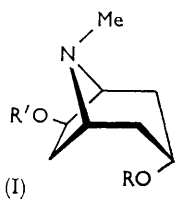
832. *The Alkaloids of the Genus* Datura, *Section Brugmansia. Part II.*[1] *New Monotigloyl Esters of the Leaves of* D. cornigera *Hook.*

By W. C. Evans and W. J. Griffin.

(−)-6β-Tigloyloxytropan-3α-ol has been identified as a minor component of the alkaloidal mixture of *Datura cornigera* leaves. Its structure was indicated by hydrolysis and confirmed by comparison with (−)-6β-tigloyloxytropan-3α-ol prepared by partial synthesis. The presence of (−)-3α-tigloyloxytropan-6β-ol in the plant is suggested.

In Part I,[1] the aerial parts of *Datura cornigera* Hook were shown to contain hyoscine as the principal alkaloid, together with smaller quantities of noratropine and other unidentified bases. In addition to the above alkaloids, the roots contain (−)-3α,6β-ditigloyloxytropane, 3,6-ditigloyloxytropan-7-ol, hyoscyamine, atropine, norhyoscyamine and (+)-tropane-3α,6β-diol. A more detailed investigation of the minor alkaloids of the leaves is recorded here.

The basic components of an ether extract of the leaves were liberated from an aqueous solution of their sulphates in eight fractions (A—H). Hyoscine was the principal component of fractions B and C. From D to H the fractions contained progressively less hyoscine and more noratropine, together with small quantities of other bases, one of which, by fractional elution from a phosphate buffer–kieselguhr column, was isolated as a colourless lævorotatary gum. This base afforded a crystalline hydrobromide, $C_{13}H_{21}NO_3$,HBr and a picrolonate, $C_{13}H_{21}NO_3$,$C_{10}H_8N_4O_5$. Its yield from the leaves was 0·012% and it comprised about 5% of the total alkaloids.



(I)

Complete hydrolysis of the base with aqueous-ethanolic barium hydroxide yielded (+)-tropane-3α,6β-diol (I; R = R′ = H) and tiglic acid. The yield of the latter indicated a monotigloyl ester and this was confirmed by the ultraviolet absorption of the alkaloid hydrobromide, maximum at 217 mμ (ε 12,600). Meteloidine and 3,6-ditigloyloxytropan-7-ol[2] exhibit the same maximum (ε 12,200 and 23,900, respectively). Esterification of the base with tigloyl chloride yielded (−)-3α,6β-ditigloyloxytropane (I; R = R′ = Me·CH:CMe·CO).

(−)-3α-Tigloyloxytropan-6β-ol was prepared by the method[3] for partial hydrolysis of diacyloxytropanes by means of dilute aqueous alkali in the presence of a water-miscible organic solvent not containing hydroxyl groups. Its hydrobromide was not similar to the hydrobromide derived from the plant alkaloid. Partial esterification of (+)-tropane-3α,6β-diol afforded two monotigloyl esters, (−)-3α-tigloyloxytropane-6β-ol and the alternative isomer, clearly (−)-6β-tigloyloxytropan-3α-ol. The latter was identical with the alkaloid obtained from *D. cornigera* (I; R = H, R′ = Me·CH:CMe·CO).

(−)-3α-Tigloyloxytropan-6β-ol was also tentatively identified as present in the plant (0·0003%) by its R_F value and conversion into the ditigloyl ester.

Experimental

Extraction of the Alkaloids.—The powdered aerial shoots (3·3 kg.) were mixed with calcium hydroxide (100 g.), moistened with water (1·5 l.), and, after 2 hr., exhaustively extracted by percolation with ether (33 l.). Removal of the solvent afforded a green, oily residue (95 g.) which was redissolved in ether and transferred to a column prepared from kieselguhr (200 g.) and 5N-sulphuric acid (100 ml.). Pigments and fats were collected in ether, and the alkaloids were recovered in chloroform from the extruded column, made alkaline by concentrated ammonia solution. Removal of the chloroform left a green syrup (19·2 g.) which, on neutralisation with

[1] Part I, Evans and Than, *J. Pharm. Pharmacol.*, 1962, **14**, 147.
[2] Evans and Partridge, *J.*, 1957, 1102.
[3] Fodor, Vincze, Tóth, Janzsó, and Lang, U.S.P. 2,905,687; B.P. 824,623.

N-sulphuric acid indicated a basic equivalent of 11·1 g. of hyoscine. The aqueous solution was washed with chloroform and the bases, liberated by successive additions of N-sodium hydroxide (3 × 5 ml., 3 × 10 ml., finally excess), were collected in chloroform. The fractions, after removal of the solvent, were designated A (chloroform washings) (3·4 g.), B (2·6 g.), C (2·0 g.), D (2·0 g.), E (1·3 g.), F (1·7 g.), G (1·4 g.), H (0·5 g.). Thin-layer chromatography with alumina and ether–ethanol (1 : 1) indicated that hyoscine was the principal component of fractions B and C, and that fractions D—H contained decreasing amounts of hyoscine and increasing amounts of noratropine. Fractions D—H contained also unidentified alkaloids.

Fraction E was transferred to kieselguhr (50 g.) loaded with 0·5M-phosphate buffer (25 ml.; pH 7·2). The ether eluate was collected in two fractions, the first of which furnished hyoscine (0·17 g.) and the second (E_1) a mixture of two bases. Continued elution of the column with chloroform and then ammoniacal chloroform gave a mixture of bases from which noratropine (0·23 g.) was isolated. Fraction E_1 on alumina (50 g.) gave, by elution with ether–ethanol (95 : 5), a gum (0·22 g.) which in ethanolic hydrobromic acid and ether afforded a *hydrobromide*, crystallising from ether–ethanol as needles, m. p. 185° (Found: C, 48·7; H, 6·6; N, 4·4. $C_{13}H_{21}NO_3$,HBr requires C, 48·75; H, 6·9; N, 4·4%), $\lambda_{max.}$ 217 mμ (ε 12,600) in EtOH. A similar treatment of fractions D, F, and G gave a total yield of 0·4 g. of this alkaloid (0·012%).

The base was recovered from the hydrobromide as a colourless gum, $[\alpha]_D^{20}$ −28·1° (*c* 1·64 in $CHCl_3$, l 5 cm.). Treatment of the hydrobromide in water with saturated aqueous picrolonic acid furnished a *picrolonate*, yellow needles (from aqueous ethanol), m. p. 187° (Found: C, 54·5; H, 5·4. $C_{13}H_{21}NO_3$,$C_{10}H_8N_4O_5$ requires C, 54·9; H, 5·8%).

Hydrolysis.—The new base (0·03 g.) in ethanol (3 ml.) was heated in a sealed tube with a solution of barium hydroxide (0·6 g.) in water (10 ml.) at 100° for 3 hr. From the mixture, acidified with 10N-sulphuric acid, ether removed tiglic acid (0·008 g., 65%), m. p. and mixed m. p. 61°, with an infrared absorption spectrum identical with that of authentic tiglic acid. The aqueous suspension was neutralised by addition of barium carbonate, then centrifuged, and the supernatent liquid was evaporated to dryness under reduced pressure. Dissolved in water and treated with sodium picrate solution, the residue afforded (+)-tropane-3α,6β-diol picrate, m. p. and mixed m. p. 252—253° (Found: C, 43·1; H, 4·4. Calc. for $C_8H_{15}NO_2$,$C_6H_3N_3O_7$: C, 43·5; H, 4·7%).

Esterification with Tigloyl Chloride.—The new hydrobromide (0·025 g.) was esterified with tigloyl chloride (0·010 g.), and the picrate prepared as previously described [4] for ditigloyl derivatives. It furnished (−)-3α,6β-ditigloyloxytropane picrate (0·030 g.), m. p. and mixed m. p. 152° (Found: C, 52·3; H, 5·55. Calc. for $C_{18}H_{27}NO_4$,$C_6H_3N_3O_7$: C, 52·4; H, 5·5%).

(−)-3α-*Tigloyloxytropan*-6β-*ol and its Derivatives.*—The 6β-tigloyl ester group of (−)-3α,6β-ditigloyloxytropane (0·020 g.) was selectively hydrolysed by the method of Fodor and his co-workers [3] and submitted to chromatography on kieselguhr (20 g.) loaded with 0·5M-phosphate buffer (15 ml.; pH 6·8). Unchanged ditigloyl ester (0·15 g.) was recovered from the ether eluate and, from the chloroform eluate, the monotigloyl ester (0·045 g.) was obtained. The latter, neutralised with dilute sulphuric acid and treated with sodium picrate, yielded a *picrate*, needles (from aqueous ethanol), m. p. 156° (Found: C, 48·9; H, 5·0. $C_{13}H_{21}NO_3$,$C_6H_3N_3O_7$ requires C, 48·7; H, 5·1%). The base in ethanolic hydrobromic acid and diluted with ether afforded a *hydrobromide*, needles (from ether–ethanol), m. p. 195° (Found: C, 49·0; H, 7·1. $C_{13}H_{21}NO_3$,HBr requires C, 48·7; H, 6·9%). The mixed m. p. of the hydrobromide with that of the natural isomer was depressed and the infra-red spectra of the two compounds were dissimilar.

(−)-6β-*Tigloyloxytropan*-3α-*ol and its Derivatives.* (+)-Tropane-3α,6β-diol picrate (0·24 g.) and tigloyl chloride (0·075 g.) were refluxed at 90° for 3 hr. and basic material was recovered in chloroform; paper chromatography indicated a mixture of the mono- and di-tigloyl esters which were transferred to kieselguhr (10 g.) loaded with 0·25M-phosphate buffer (3·2 ml.; pH 6·1). (−)-3α,6β-Ditigloyloxytropane (0·045 g.) was recovered from the ether eluate, and the monotiglic esters (0·022 g.) were eluted in chloroform. The monoesters were resubmitted to chromatography at pH 6·8; from the ether eluate a gum (0·009 g.) was obtained which, dissolved in ethanolic hydrobromic acid and diluted with ether, afforded a hydrobromide (0·008 g.), needles (from ether–ethanol), m. p. and mixed m. p. with the monotigloyl ester derived from plant material 184°. The natural and the synthetic hydrobromide had identical

[4] Evans and Wellendorf, *J.*, 1958, 1991.

infrared absorption spectra. Continued elution of the column with chloroform gave (−)-3α-tigloyloxytropan-6β-ol (0·009 g.), identified as the picrate, m. p. 156°, undepressed on admixture with the picrate of the isomer prepared by partial hydrolysis of the ditigloyl ester (Found: C, 49·0; H, 5·1%).

The R_F values for the 6β- and 3α-tiglic esters on thin-layer alumina chromatograms were (ether–ethanol 1 : 1) 0·70 and 0·36, respectively, and (chloroform–ethanol 1 : 1) 0·75 and 0·6, respectively.

Other Bases of the Plant Extract.—From the chloroform eluate of fraction E and corresponding fractions of D, F, and G small quantities of mixed bases were obtained after the removal of most of the noratropine; some components had R_F 0·3—0·4 on thin layer alumina chromatograms (ether–ethanol 1 : 1). By repeated chromatography on alumina columns (ether–ethanol 50 : 50; 95 : 5; 75 : 25), 6β-tigloyloxytropan-3α-ol and noratropine were removed, but a mixture of two alkaloids with R_F values of 0·6 and 0·57 on alumina plates (chloroform–ethanol 1 : 1) could not be resolved. The mixture (0·025 g.) was esterified with tigloyl chloride (0·03 g.) in the usual manner and the extracted bases were transferred to alumina (10 g.). From the ether eluate, (−)-3α,6β-ditigloyloxytropane (0·012 g.) was obtained, [picrate, needles (from aqueous ethanol), m. p. and mixed m. p. 149—150°], identical in infrared absorption with authentic material. Chloroform eluted a base (0·016 g.) which gave a positive Vitali–Morin reaction and furnished a picrate, needles (from aqueous ethanol), m. p. 163. It was not similar to the product of the treatment of either atropine or hyoscyamine with tigloyl chloride.

This work has been assisted by a grant from the Medical Research Council, London.

THE DEPARTMENT OF PHARMACY, UNIVERSITY OF NOTTINGHAM. [*Received, April 5th,* 1963.]