THE STRUCTURES OF THE PYRROLIZIDINE ALKALOIDS NEOPLATYPHYLLINE AND HASTACINE*

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Neoplatyphylline, $C_{18}H_{27}NO_5$, was isolated from mother liquors resulting from the preparation of platyphylline (I) from *Senecio rhombifolius* (Willd.) Sch. Bip. (formerly regarded as *S. platyphyllus* (Bieb.) DC.) on an industrial scale.[1] Alkaline and acid hydrolyses were said to give the same products as from platyphylline, which is an ester of platynecine with senecic acid. Hastacine, also $C_{18}H_{27}NO_5$, was obtained from *Cacalia hastata*,[2] another species of the tribe Senecioneae, family Compositae. It gave on hydrolysis a saturated diol, hastanecine, isomeric with platynecine, and a dicarboxylic acid, $C_{10}H_{16}O_5$, with properties similar to those later observed for integerrinecic acid. The structures of these two alkaloids have now been clarified in conjunction with a parallel study on the stereochemistry of the saturated pyrrolizidine diols.[3]

In regard to signals due to the protons of the esterifying acids, the nuclear magnetic resonance spectra of neoplatyphylline and hastacine are closely similar to the spectrum of platyphylline, except for the chemical shift of the CH_3–C**H**=C(–CO–) proton, δ 6·58 for neoplatyphylline, δ 6·72 for hastacine, and δ 5·83 for platyphylline. These shifts indicate that the first two bases have a *trans*-ethylidene group in the esterifying acid. This indication was confirmed by the alkaline hydrolysis of the alkaloids which led in each instance to integerrinecic acid. It follows that neoplatyphylline is (II), an ester of platynecine with integerrinecic acid, but elucidation of the complete structure of hastanecine requires consideration also of the nature of hastanecine.

The saturated pyrrolizidine diols, platynecine (III) and dihydroxyheliotridane (IV), are known to be the two possible 7,9-diols with 1β-hydroxymethyl-8α configuration. Apart from hastanecine, there are three other saturated diols which might be the unknown 7,9-diols of 1α-hydroxymethyl-8α configuration: turneforcidine, macronecine, and the amino alcohol from retusine.[4] Untch and Martin[5] have recently reported a synthesis of the unknown 7,9-diols in their enantiomeric form (1β-hydroxymethyl-8β configuration) and stated that their properties agree with those reported

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[1] Danilova, A. V., Utkin, L. M., Kozyreva, G. V., and Syrneva, Yu. I., *Zh. obshch. Khim.*, 1959, **29**, 2432 (Eng. transln, p. 2396).

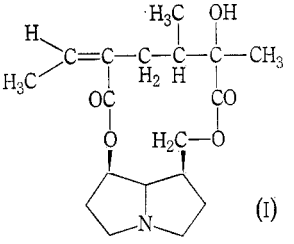
[2] Konovalov, V. S., and Men'shikov, G. P., *Zh. obshch. Khim.*, 1945, **15**, 328.

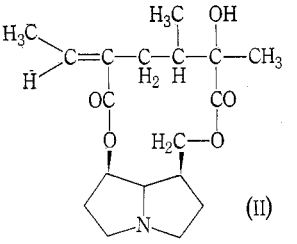
[3] Culvenor, C. C. J., Smith, L. W., Aasen, A. J., and Sawhney, R. S., unpublished data.

[4] Culvenor, C. C. J., and Smith, L. W., *Aust. J. Chem.*, 1957, **10**, 464.

[5] Untch, K. G., and Martin, D. J., 52nd A. Rep. Mellon Inst., 1965, p. 11.

for hastanecine and turneforcidine. We find that the mass spectra of hastacine and hastanecine are in agreement with this report, the close similarity of the former to the spectra of platyphylline and neoplatyphylline and of the latter to the spectrum of platynecine, being consistent only with diastereoisomeric relationships (cf. data listed in the Experimental section). The mass spectra of these compounds are discussed in more detail by Culvenor *et al.*[3] who show, by means of a comparison of the n.m.r. spectra of the four 7,9-diols and their parent alkaloids, that hastanecine has the configuration 7β-hydroxy-1α-hydroxymethyl-8α-pyrrolizidine (V). The amino alcohol from retusine is identical with turneforcidine, which is 7α-hydroxy-1α-hydroxymethyl-8α-pyrrolizidine, and macronecine is 2β-hydroxy-1β-hydroxymethyl-8β-pyrrolizidine.[3] The structure of hastacine is therefore (VI).


(I)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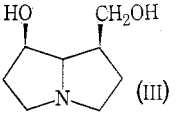
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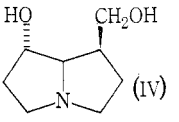
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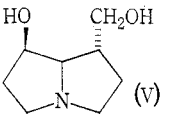
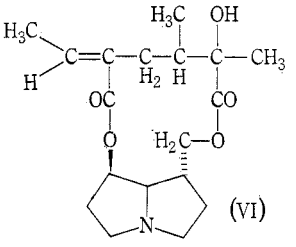
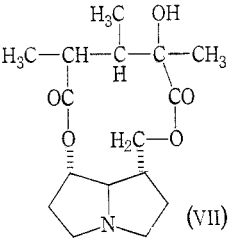

(V)


(VI)


(VII)

The n.m.r. spectra of neoplatyphylline and hastacine show the widely spaced AB system for the H 9 protons typical of the macrocyclic diester alkaloids. A feature of the spectrum of hastacine is the remarkably high-field position, δ *c.* 4·4, of the C**H**–O–CO signal which is normally about δ 5·0.[6] This proton is not exhibiting the normal acylation shift of secondary esters, an effect which must be ascribed to strain in the macrocyclic ring preventing the secondary ester grouping from assuming its preferred conformation with the atoms H–C–O–CO–C coplanar.[7] Hastacine and retusine (VII)[3]

[6] Culvenor, C. C. J., and Woods, W. G., *Aust. J. Chem.*, 1965, **18**, 1625.
[7] Culvenor, C. C. J., *Tetrahedron Lett.*, 1966, 1091.

are the only known macrocyclic pyrrolizidine diesters with the unfavourable 1α-acyloxymethyl configuration, and it is not surprising that the macrocyclic ring should be more highly strained than in other related diesters.

Experimental

Analyses were made by the Australian Microanalytical Service, Melbourne. The solvent used in paper chromatography was the upper phase resulting from shaking n-butanol with an equal volume of 5% acetic acid.

Hydrolysis of Neoplatyphylline

Neoplatyphylline (77 mg) was refluxed for 2 hr with a solution of barium hydroxide in 20 ml H_2O. The solution was cooled, and barium carbonate was precipitated with CO_2 and removed by filtration. The filtrate was made acid to Congo red and continuously extracted with ether for 8 hr. Evaporation of the extract gave crystalline integerrinecic acid (34 mg). Recrystallization from ethyl acetate gave colourless prisms, m.p. 146–147°, undepressed on admixture with authentic integerrinecic acid, $[\alpha]_D^{18}$ +11·6 (*c*, 0·38 in EtOH) (Found: C, 55·3; H, 7·5. Calc. for $C_{10}H_{16}O_5$: C, 55·5; H, 7·5%). The acid had i.r. and n.m.r. spectra identical with those of integerrinecic acid.

The aqueous mother liquor remaining after extraction of the integerrinecic acid was run through a column of Amberlite CG400 anion-exchange resin. Elution with H_2O and evaporation of the eluate gave crystalline platynecine (32 mg), which on crystallization from acetone gave colourless prisms, m.p. 147–148°, undepressed on admixture with authentic platynecine, R_F 0·21.

Hydrolysis of Hastacine

Hastacine (60 mg) was hydrolysed by the method used for neoplatyphylline. The acidic product (33 mg), recrystallized from ethyl acetate, gave colourless prisms, m.p. 149–149·5°, undepressed on admixture with authentic integerrinecic acid, $[\alpha]_D^{18}$ +8·5° (*c*, 0·41 in EtOH). The acid had i.r. and n.m.r. spectra identical with those of integerrinecic acid.

The basic product, hastanecine (25 mg), was recrystallized from acetone to give colourless prisms, m.p. 113–114°, $[\alpha]_D^{20}$ −10·0° (*c*, 0·43 in EtOH), R_F 0·17 (lit.[2] m.p. 113–114°, $[\alpha]_D$ −9·1° (MeOH)).

Mass Spectra

m/e values and intensities, recorded on a Hitachi Perkin–Elmer RMU 6D instrument with direct entry of samples into the ion chamber, were as follows:

Platyphylline, 337 (27), 322 (3), 320 (3), 266 (5), 252 (3), 239 (3), 238 (3), 226 (12), 222 (7), 220 (3), 212 (10), 211 (60), 180 (8), 156 (5), 141 (12), 140 (100), 139 (15), 138 (64), 125 (12), 124 (10), 123 (55), 122 (63), 121 (10), 120 (10), 110 (5), 109 (9), 108 (14), 97 (5), 96 (29), 95 (15), 94 (5), 83 (12), 82 (98), 81 (11), 80 (10).

Neoplatyphylline, 337 (27), 322 (3), 320 (3), 266 (5), 252 (2), 239 (3), 238 (3), 226 (8), 222 (6), 220 (3), 212 (8), 211 (53), 210 (4), 180 (12), 156 (4), 141 (11), 140 (96), 139 (13), 138 (52), 125 (12), 124 (9), 123 (55), 122 (65), 121 (14), 120 (12), 110 (5), 109 (9), 108 (14), 97 (4), 96 (26), 95 (16), 94 (5), 83 (12), 82 (100), 81 (11), 80 (10).

Hastacine, 337 (33), 322 (2), 320 (3), 294 (3), 293 (11), 266 (2), 239 (4), 238 (7), 226 (6), 222 (6), 220 (2), 212 (9), 211 (49), 210 (4), 180 (4), 156 (4), 153 (7), 149 (3), 141 (14), 140 (100), 139 (10), 138 (47), 124 (13), 123 (53), 122 (59), 121 (14), 120 (14), 110 (5), 109 (8), 108 (11), 106 (39), 97 (4), 96 (26), 95 (16), 94 (6), 93 (5), 83 (11), 82 (90), 81 (11), 80 (9).

Platynecine, 157 (17), 156 (1), 140 (1), 138 (1), 126 (3), 114 (5), 113 (36), 108 (3), 106 (1), 100 (4), 99 (3), 98 (1), 96 (2), 94 (2), 86 (2), 85 (1), 83 (10), 82 (100), 81 (3), 80 (5).

Hastanecine, 157 (17), 156 (1), 140 (1), 138 (1), 126 (3), 114 (13), 113 (37), 108 (2), 106 (1), 100 (1), 99 (4), 98 (2), 96 (2), 94 (2), 86 (1), 83 (10), 82 (100), 81 (3), 80 (5).