Tetrahedron, 1964, Vol. 20, pp. 581 to 583. Pergamon Press Ltd. Printed in Northern Ireland

THE STEREOCHEMISTRY OF LIMASPERMINE, HAPLOCINE AND HAPLOCIDINE

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(*Received* 13 *September* 1963; *in revised form* 17 *October* 1963)

Abstract—Haplocine has been transformed by a sequence of chemical steps into palosine, identical with material synthesized from aspidospermine. This conversion provides unambiguous proof of the stereochemistry of haplocine, haplocidine and limaspermine.

THE isolation of two new alkaloids, haplocine (Ia) and haplocidine (Ic) from *Haplophyton cimicidum* (Apocynaceae) was recently reported.[1] In the course of the structure proof of these bases, haplocidine and haplocine were interconverted, and haplocine was reduced either catalytically or by sodium borohydride to afford a dihydro derivative identical with the alkaloid limaspermine (IIa) from *Aspidosperma limae*.[2] In order to obtain evidence concerning the stereochemistry of haplocine and haplocidine, the conversion of haplocine, via limaspermine derivatives, into a compound which should be either the alkaloid palosine (IIe) or a stereoisomer of palosine was undertaken.

Methylation of haplocine (Ia) with dimethyl sulfate in aqueous sodium hydroxide afforded, in high yield, O-methylhaplocine (Ib), m.p. 240–241°. Catalytic reduction of Ib in the presence of a platinum catalyst gave O-methyllimaspermine (IIb) which was obtained crystalline only in the form of an acetone solvate, m.p. 100°. The reaction of IIb with tosyl chloride in pyridine gave the corresponding amorphous tosylate (IIc) which was converted by sodium thiophenolate in warm dimethyl sulfoxide to a crystalline C-21 thiophenyl ether (IId), m.p. 161°. Raney nickel desulfurization of sulfide IId in refluxing benzene afforded palosine (IIe), m.p. 150–151°, identical with authentic palosine prepared from aspidospermine (IIf) by acid hydrolysis followed by propionylation.[3]

Since the complete stereochemistry of aspidospermine rests upon the firm basis of X-ray analysis,[4] the transformations described above serve to define uniquely the stereochemistry of limaspermine as shown in structure IIa;[5] haplocine and haplocidine must therefore be represented sterically as Ia and Ic.[6,7]

[1] M. P. Cava, S. K. Talapatra, K. Nomura, J. A. Weisbach, B. Douglas and E. C. Shoop, *Chem. Ind.* 1242 (1963).

[2] M. Pinar, W. von Philipsborn, W. Vetter and H. Schmid, *Helv. Chim. Acta* **45**, 2260 (1962).

[3] W. I. Taylor, H. Lehner and J. Schmutz, *Helv. Chim. Acta* **42**, 2250 (1959).

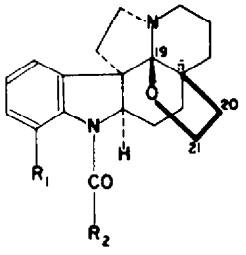
[4] J. F. D. Mills and S. C. Nyburg, *J. Chem. Soc.* 1458 (1960).

[5] In an independent investigation, the stereochemistry of limaspermine has been correlated with that of aspidospermine via a transformation product of cylindrocarpine: M. Pinar and H. Schmid, *Liebigs Ann.* in press. We are grateful to Prof. Schmid for kindly communicating his results to us prior to publication.

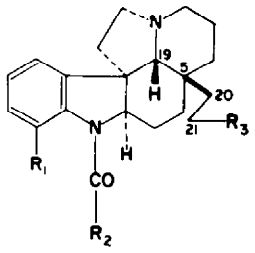
[6] Models show that if C-20 of the oxyetheno bridge is attached β to C-5, the oxygen atom of this bridge can only be attached β to C-19. In other words, the bridge must be *cis*-fused at C-5 and C-19.

[7] Prof. C. Djerassi has informed us of the isolation of an alkaloid from *Vallesia dichotoma* which, though as yet amorphous, appears to be identical with haplocidine. This substance has now been stereochemically correlated with a cylindrocarpine degradation product: K. S. Brown, Jr., H. Budzikiewisz and Carl Djerassi, *Tetrahedron Letters* 1731 (1963). We thank Prof. Djerassi for kindly informing us of this work prior to publication.

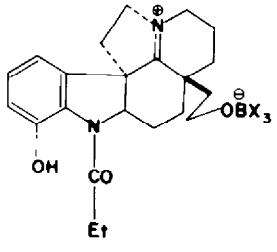
It is worthy of note that the catalytic hydrogenolysis of either O-methylhaplocine or of haplocine itself[1] appears to be a highly stereospecific process, as determined both by product isolation and by thin layer chromatography. Apparently delivery of hydrogen from the catalyst surface takes place only at the less hindered β-face of the molecule. In contrast, the sodium borohydride reduction of haplocine gives in addition to limaspermine[1] as the major product, a small amount of a second product which is probably 19-epilimaspermine.[8] The formation of this isomer in the borohydride reduction is not unexpected since in this reaction ring opening to a complex immonium species (III), more exposed than Ia to α-attack, probably precedes the actual reduction step.



Ia: $R_1 = OH$, $R_2 = Et$
Ib: $R_1 = OMe$, $R_2 = Et$
Ic: $R_1 = OH$, $R_2 = Me$



IIa: $R_1 = OH$, $R_2 = Et$, $R_3 = OH$
IIb: $R_1 = OMe$, $R_2 = Et$, $R_3 = OH$
IIc: $R_1 = OMe$, $R_2 = Et$, $R_3 = OTs$
IId: $R_1 = OMe$, $R_2 = Et$, $R_3 = SC_6H_5$
IIe: $R_1 = OMe$, $R_2 = Et$, $R_3 = H$
IIf: $R_1 = OMe$, $R_2 = Me$, $R_3 = H$



III

EXPERIMENTAL

Analyses were carried out by Dr. A. Bernhardt, Mülheim. M.ps. are uncorrected.

O-Methylhaplocine (Ib). To a solution of haplocine (Ia, 0·57 g) in 1N HCl aq. (20 ml) was added slowly 20% NaOH aq. (13 ml). The precipitate which formed dissolved completely when the suspension was diluted with water (30 ml). To the solution was added dimethyl sulfate (1 ml) and the mixture was stirred at room temp for 6 hr, additional portions of dimethyl sulfate (1 ml) and 20% NaOH (2 ml) being added every 30 min. The insoluble product was washed with water and crystallized from methanol to give colorless plates of Ib (0·57 g), m.p. 238–239°. The analytical sample, m.p. 240–241°, $[\alpha]_D^{20}$ +5° (*c*, 1·25 in $CHCl_3$), was obtained by recrystallization from methanol. (Found: C, 72·43; H, 7·99; N, 7·12. Calc. for $C_{22}H_{30}N_2O_3$: C, 72·22; H, 7·91; N, 7·32%).

O-Methyllimaspermine (IIb). A solution of O-methylhaplocine (Ib, 0·44 g) in ethyl acetate (150 ml) was hydrogenated at room temp. and atm. press. in the presence of a small amount of prereduced platinum oxide catalyst; after 7 hr one molar equivalent of hydrogen had been absorbed.

[8] Unpublished experiments of S. K. Talapatra.

The catalyst was removed by filtration and the solvent removed to give an oily residue, which was purified by solution in dil. HCl aq. followed by basification with ammonia and extraction into ether. Evaporation of the dried ethereal solution followed by crystallization from acetone–hexane mixture afforded IIb (0·40 g) as the acetone solvate, m.p. 98–100°. A sample which was further purified by chromatography over alumina (Woelm, Neutral I) followed by crystallization from acetone–hexane had essentially the same m.p. (100°). When the crystals were dried under vacuum to constant weight acetone was lost (disappearance of IR peak at 5·88 μ) and the material became amorphous. Analysis was performed on unsolvated IIb, m.p. 170°, $[\alpha]_D^{29}$ +89° (*c*, 0·823 in $CHCl_3$). (Found: C, 71·26; H, 8·47; N, 7·32. Calc. for $C_{23}H_{32}N_2O_3$: C, 71·84, H, 8·39; N, 7·29%).

21-*Thiophenylpalosine* (IId). A solution of O-methyllimaspermine (IIb, 0·405 g) and *p*-toluenesulfonyl chloride (0·20 g) in pyridine (10 ml) was allowed to stand at room temp. under nitrogen for 20 hr. The solution was poured into ice and water and the product isolated, after the addition of ammonia, by ether extraction. The resulting crude tosylate (0·53 g), which could not be obtained crystalline, was dissolved in dry dimethyl sulfoxide (7 ml) and added to dry sodium thiophenolate prepared by evaporating a methanolic solution (10 ml) of thiophenol (0·35 ml) and sodium hydroxide (0·13 g). The mixture was heated under nitrogen on the steam bath for 3 hr, and then poured into cold water. Extraction with ether, followed by work-up in the usual manner afforded sulfide IId as yellow needles (0·37 g), m.p. 158–160°, on crystallization from absolute ethanol. The recrystallized analytical sample, m.p. 161°, $[\alpha]_D^{28}$ −71 (*c*, 1·03 in $CHCl_3$), formed colorless needles. (Found: C, 72·96; H, 7·82; N, 5·95. Calc. for $C_{29}H_{36}O_2N_2S$: C, 73·08; H, 7·61; N, 5·88%).

Conversion of sulfide IId *into palosine* (IIe). To a solution of sulfide IId (0·15 g) in benzene (20 ml) was added freshly prepared Raney nickel (ca. 0·5 g, washed well with water, ethanol, and then benzene). The mixture was refluxed under nitrogen on the steam bath for 4 hr. Evaporation of the filtered solution gave an oil which crystallized from acetone–hexane as needles (0·08 g), m.p. 146–148°. Chromatography of the product over alumina (Woelm, Neutral I) and subsequent crystallization from hexane afforded colorless needles of palosine (IIe), m.p. 150–151°, $[\alpha]_D^{30}$ −82° (*c*, 0·943 in $CHCl_3$). This material was identical (m.p., mixed m.p., IR spectrum and rotation) with authentic palosine prepared from aspidospermine.

Palosine (IIe) *from aspidospermine* (IIf). A solution of aspidospermine (IIf, 1·00 g) in 10% HCl aq. (40 ml) was refluxed under nitrogen for 5 hr. The basic product was isolated in the usual manner and crystallized from dilute acetone to give deacetylaspidospermine (0·77 g), m.p. 106–107°. A portion of the deacetylaspidospermine (0·18 g) was dissolved in pyridine (5 ml) containing propionyl chloride (0·4 ml), and the resulting solution kept under nitrogen at room temp for 2 hr, and then heated for 10 min on the steam bath. After the usual work-up, the basic product was chromatographed over alumina (Woelm, Neutral I) in benzene. Crystallization of the eluted material from hexane afforded palosine (0·12 g), m.p. 150–151°.

Palosine was found to crystallize from acetone or acetone–hexane mixture as an acetone solvate (as determined by IR analysis). The crystals lost their solvent of crystallization on standing at room temp. for several weeks, or on drying under vacuum at 80° for 24 hr.

Acknowledgement—We are grateful to the National Institutes of Health for a grant (GM 05640) in support of this work.