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THE STRUCTURE OF ISOPILOCEREINE

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CHEMICAL structures of pilocereine[1] and piloceredine[2], the alkaloids isolated from Lophocereus schottii and some other giant cacti, have been studied by C. Djerassi and his co-workers who proposed the structure Ia, $C_{30}H_{44}O_4N_2$[3], for these alkaloids. This structure (Ia) is dimeric form of lophocerine (IIa) which has been isolated from the same origin[2]. It has been established that piloceredine is diastereoisomer of pilocereine and both are forming racemate.

In the course of structure elucidation of pilocereine, Djerassi et al found that the treatment of pilocereine with metallic potassium in liquid ammonia gave a new crytophenolic base, $C_{30}H_{44}O_4N_2$, which was assumed to be a rearranged product. They named it isopilocereine and postulated structure III. We had some questions about this rearrangement and reexamined the structure of isopilocereine.

When treated with K in liq.NH_3, O-methylisopilocereine, which we

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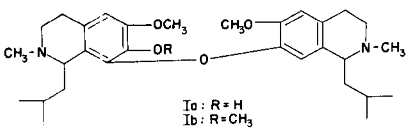
[1] G. Heyl, Arch. Pharm. 239, 451 (1901); C. Djeressi, N. Frick and L.E. Geller, J. Amer. Chem. Soc. 75, 3632 (1953).

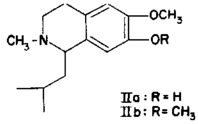
[2] C. Djerassi, T. Nakano and J.M. Bobbitt, Tetrahedron 2, 58 (1958).

[3] C. Djerassi, S.K. Figdor, J.M. Bobbitt and F.X. Markeley, J. Amer. Chem. Soc. 79, 2203 (1957).

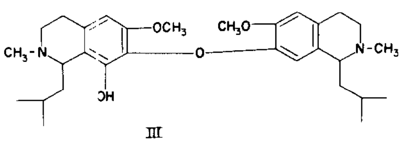
could obtain in crystalline form, m.p.91-92°, afforded IIa and IIb in quantitative yields. This suggested that the structure of O-methylisopilocereine should be Ib or IV. However, Ib could be left out of consideration because only two racemic diastereoisomers are possible for the structure Ib and O-methylpilocereine and O-methylpiloceredine had already been assigned to them. Accordingly, O-methylisopilocereine was considered to be IV. In order to verify this assumption, we tried to synthesize Ib and IV.



Ia : R = H
Ib : R = CH₃



IIa : R = H
IIb : R = CH₃



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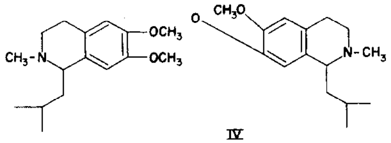
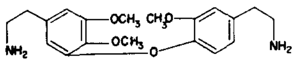


IV

Compound VI was synthesized by Schotten-Baumann condensation of the amine V with isovaleryl chloride followed by Bischler-Napieralski cyclization. This was reduced with sodium borohydride to give tetrahydro compound as a mixture of diastereoisomers. A small amount of crystalls, which was believed to be one of the racemic diastereoisomers, could be separated by recrystallization of the crude product from ether-cyclohexane. This substance was N-methylated to give a crystalline base m.p. 122-123° (S-B), (Found: C, 73.06; H, 9.04; N, 5.47. $C_{31}H_{46}O_4N_2$ requires C, 72.90; H, 9.08; N, 5.49). Non-identity of the substance with O-methylpilocereine was established by I.R. comparison, mixture melting point and paper chromatography. However, it was found that I.R. spectrum ($CHCl_3$) and Rf value were quite identical with those of O-methylisopilocereine, though mixture melting point showed remarkable depression. N-methylation of the crude tetrahydro compound gave an oily base (S-base) which was also assumed to be a mixture of diastereoisomers and showed quite the same I.R. spectrum in solution with S-B. In this synthetic route, however, it would be possible to form VII instead of Ib. So, the proof of the structure (Ib) of the S-base was provided by K-liq.NH_3 reaction, where IIa and IIb were obtained in quantitative yields.



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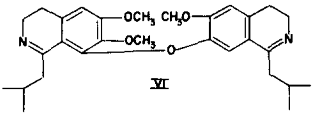

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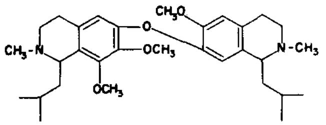
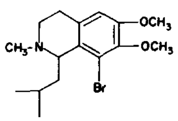


VII



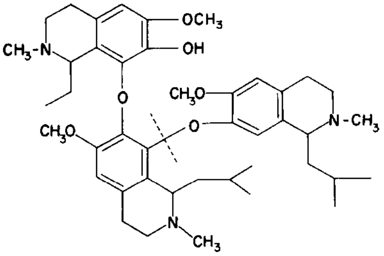
VIII

Then another route of synthesis of Ib was tried. IIa and VIII were subjected to Ullmann reaction and the oily product was chromatographed repeatedly on alumina to result in separation of two crystalline substances. The substance, m.p. 89-91° (U-A) (Found: C, 73.10; H, 9.26; H, 5.41.), which was obtained from earlier fractions showed no depression on admixture with O-methylisopilocereine (m.p. 91-92°) and I.R. spectra (KBr, $CHCl_3$) were also quite identical with those of the latter. Another substance, m.p. 122-123° (U-B), (Found: C, 72.99; H, 9.30; N, 5.71.), obtained from later fractions, was identified with S-B (m.p. 122-123°) by mixture melting point and I.R. comparison (KBr, $CHCl_3$). Furthermore, it was found that I.R. spectrum of U-A in $CHCl_3$ was quite coincident with that of U-B.

From these results, it is reasonable to conclude that the structure of O-methylisopilocereine is Ib and S-B (=U-B) is probably its diastereoisomer, and that the structure of pilocereine and of piloceredine is not Ia.

Recently we received a private communication from Dr. Djerassi, informing us that he corrected the structure of pilocereine to IX, $C_{45}H_{65}O_6N_3$, which is the trimeric form of lophocerine (IIa), on the basis of mass spectra and N.M.R. of pilocereine and its derivatives.

Adopting this new formula, it is readily expected, from the results of our earlier studies on cleavages of diphenyl ethers[4], that pilocereine



IX

can be bisected with K-liq.NH_3 only at the diphenyl ether linkage having no phenolic hydroxyl group in its neibourhood to give a cryptophenolic C_{30} compound, which affords Ib on methylation.

Confirmation of the position of phenolic hydroxyl group of isopilocereine, which is supposed as Ia by colour tests and some other reasons, and synthesis of IV are now in progress.

Acknowledgement- We are indebted to Professor C. Djerassi for providing with pilocereine.

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[4] M. Tomita, Y. Inubushi and H. Niwa, Yakugaku Zasshi **72**, 206, 220 (1952).