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RETAMINE STRUCTURE, SYNTHESIS, ABSOLUTE CONFIGURATION AND CONFORMATION

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Although our revision of earlier work[2] prompted by the publication of Bohlmann et al.[1] produced results, which are in agreement with the later publication of Bohlmann et al.[3,4] on the synthesis and structure of retamine, they were obtained in a different way (with the exception of retamine oxidation by the Warnhoff and Warnhoff-Reynolds method[5] also used by Bohlmann et al.) and therefore they are worthy of publication.

The reduction of retamine to pachicarpine was accomplished by Fraga and Ribas[6] by boiling retamine dihydroiodide with hydroiodic acid and red phosphorus for several hours. As this method can bring about molecular rearrangements, it was decided to prepare retamine p-toluensulfonic ester in order to reduce it with $LiAlH_4$. It was also interesting to submit this compound to epimerization by the Bohlmann method[7] in order to confirm our previous conclusions[2] that retamine and isoretamine are epimeric.

After several unsuccessful attempts Retamine p-toluensulfonic ester was prepared in the form of the crystalline dihydrochloride m.p.178-180° and its dipicrate m.p.165°. The free base was obtained from either of these salts in the form of an unstable oil, which spontaneously transformed into $\Delta^{5(11)}$-deshydrosparteinium p-toluensulfonate. This Δ^{11}-dehydrobase was characterized as a dipcrate m.p. 230° and as a diperchlorate m.p.267-268°. These results are in complete agreement

with the structure of a 12(a)-hydroxisparteine, shown by Bohlmann et al. for Retamine and refute the earlier proposed structure of 8-hydroxy-sparteine proposed earlier,[2] Isoretamine p-toluensulfonate was also obtained in the form of a perchlorate which crystallized from methanol, m.p. 222°d.

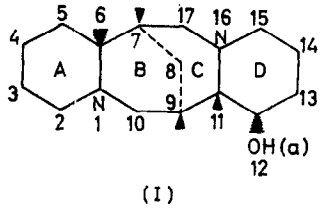
An attempt to epimerize the two p-toluensulfonic esters failed, no doubt on account of their unstability.

These results prompted the synthesis of Retamine by application of the Brown reaction[8] to Δ^{11}-dehydrosparteine. This base, although somewhat unstable, may be obtained from (+)-sparteine (pachicarpine) via Leonard et al.[9] The $\Delta^{11(12)}$-dehydrosparteinium diperchlorate, crystallizes from water m.p. 267-268° $[\alpha]_D^{21,5°}$ -23,2° (C, 2,73%, water) and its spectrum in nujol shows the two characteristic bands at 1687cm^{-1} and 3045cm^{-1}. The free base obtained under nitrogen from the diperchlorate was immediately submitted to hydroboration in the usual solvents for cis-addition (tetrahydrofurane and ether). The hydroboration product, obtained with an excess of externally generated diborane[10], was oxidized in the usual way with alkaline hydrogen peroxide, and then treated with zinc and hydrochloric acid, in order to reduce the amine oxides. In the resulting mixture of bases α-isosparteine (the most abundant), sparteine, isoretamine and another unknown compound could be identified and separated. As no Retamine was present, it was concluded that cis-hydroboration of the double bonds C_{11}-N_{16} and C_{11}-C_{12} in the enamonium-vinilamine equilibrium of the Δ^{11}- dehydrosparteine had taken place. To favour the shift of the double bond to the C_{11}-C_{12} position and improve the yield of isoretamine, the strong base triethylamine was added to the hydroboration reaction. These improved conditions yielded, besides the α-isosparteine, which continued to be the main product, retamine in

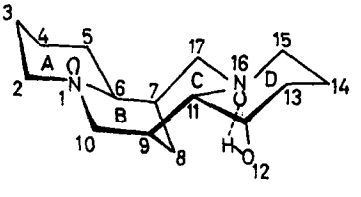
amounts higher than sparteine, isoretamine, and the fourth unknown base. The mechanism of hydroboration in the presence of triethylamine is now being investigated. The retamine was separated by the column chromatography on "Woelm" alumina of grade III, and crystallized from ethanol m.p.162-163°$[\alpha]_D^{25°}$ +41,3°(C,0,49 abs.EtOH). Its m.p. was not depressed by an authentic sample and its IR spectrum is identical with that of a pure specimen.

These results agree well with the structure of a 12(a)-hydroxysparteine, given by Bohlmann et al. for retamine [1.3.4] although the quantitative formation of α-isosparteine when the hydrochloride of retamine p-toluensulfonate ester is treated with $LiAlH_4$ in dioxan, requires elucidation. An explanation given by Professor Bohlmann, with which we agree, suggests that in this case reduction goes through the Δ^{11}-dehydrosparteine, formed by the elimination of the two axial groups, p-toluensulfonyl and H at C_{11}. This explanation is supported by the fact that isoretamine p-toluensulfonate ester (equatorial) is reduced at room temperature (15°) with $NaBH_4$, affording (+)-sparteine, in a manner similar to chlororetamine (equatorial). On the other hand, chloroisoretamine (axial) is not reduced at room temperature; it is only reduced with $LiAlH_4$ in boiling dioxan, giving a mixture of 5 products, from which α-isosparteine (main product) sparteine, Δ^{11}-dehydrosparteine and retamine were identified by thin layer chromatography. The elimination of the axial p-toluensulfonyl group in the retamine p-toluensulfonate ester is so easy that $NaBH_4$ reduction in dioxan yields α-isoparteine at room temperature.

Absolute Configuration: retamine is a derivative of (+)-sparteine, the absolute configuration of which was established by Okuda, et al.[11]. Therefore, bearing in mind the axial HO group at C_{12} retamine must have formula (1) and its seven asymmetric centres must have the following configuration: (1S:6S:7R:9R:11R:12S:16R). The C ring is boat, as suggested by Bohlmann and this conformation is probably favoured by the repulsion of the free N-electrons (in the chair conformation repulsion should be stronger) and by the intramolecular hydrogen bridge between the N_{16} and the HO group, which stabilizes the molecule. The conformation of the whole molecule may be represented by (II).



(I)



(II)

The full paper of this work shall be published in "Anales Real Sociedad Española de Física y Química"

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