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2-HYDROXY-4-PHENYLQUINOLIZIDINE

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2-Hydroxy-4-phenylquinolizidine is the fundamental structure in the skeleton of the Lythraceae alkaloids and a scheme of biosynthesis of these alkaloids was presented by Ferris et al. (1).

2-Hydroxy-4-phenylquinolizidines were synthesized and the stereoisomers were characterized. Intramolecular cyclization of N-benzoylisopelletierine to 4-phenylquinolizidine derivatives proceeded with ill success but the condensation of isopelletierine with benzaldehyde in aqueous sodium hydroxide solution at 50°C afforded a mixture of diastereoisomeric 2-oxo-4-phenylquinolizidines (I) smoothly (yield 70 %). Wolff-Kishner reduction of I gave 4-phenylquinolizidines, which were separated into the cis and trans isomers in the ratio of 2 : 1.

Catalytic hydrogenation of I (14.5 g) in the presence of Adams catalyst in acetic acid gave the diastereoisomeric mixture of 2-hydroxy-4-phenylquinolizidine (II), which was separated each other by the alumina chromatography as follows;

The first fraction (1.1 g) eluted with petroleum ether was contaminated by octahydropyrido-[1.2.C][1.3]-oxazine derivatives (III), produced from the condensation of 3-(piperidyl-2)-propanol-2, together with isopelletierine, and benzaldehyde (2,3).

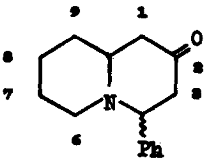
3-Methyl(e)-1-phenyloctahydropyrido-[1.2.C][1.3]-oxazine (0.5 g), purified through its picrate (m.p. 201-203°$^{+}$), showed absorption at 2750 and 2800 cm^{-1} in IR spectrum and the NMR signals at δ=1.15 (C_3-CH_3eq doublet J=6); 2.25 (C_9-H Wh=20); 3.61 (C_3-Hax sextet J=6); 4.27 (C_1-Hax singlet); 7.22 ppm. (aromatic-H). Another minor isomer, obtained by alumina chromatography of oxazine which was produced from the condensation of 3-(piperidyl-2)-propanol-2 with benzaldehyde, showed the NMR signals at 1.3 (C_3-CH_3ax doublet J=7); 2.4 (C_9-H Wh=20); 4.17 (C_3-Heq multiplet); 4.58 (C_1-Hax singlet); 7.25 ppm. (aromatic-H).

The second fraction eluted with petroleum ether contained the trans isomers. Isomer IIB (3.3 g, b.p. 155-157°/0.001 mmHg$^+$; its picrate, m.p. 230-232°$^+$) exhibited Bohlmann bands in IR spectra and the NMR signals at 2.95 (OH singlet); 2.6-2.75 (2H broad); 3.5 (C_2-H Wh=20); 7.17 (aromatic-H); its acetate, C_2-H 4.70 ppm. Although another isomer IIA existing in earlier eluted parts was not isolated in pure form due to its poor yield, it showed the NMR signals at 2.85 (OH singlet); 3.85 (C_2-H Wh=15); 7.10 (aromatic-H); its acetate, C_2-H 4.90 ppm. Another fraction gave a mixture of isomer A and B (2.0 g).

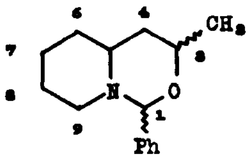
The carbinol proton of the isomer IIB absorbed at a higher field and had a greater band width (Wh=band width at one-half of the peak height, c.p.s.) than its corresponding isomer IIA (4). Therefore it is suggested that the conformation of the isomer IIA is expressed as 2-hydroxy(a)-4-phenyl(e)-trans-quinolizidine, while the isomer IIB is assigned 2-hydroxy(e)-4-phenyl(e)-trans-quinolizidine.

Other two isomers eluted in the later fractions with petroleum ether-ether is suggested as cis-quinolizidine because of absence of absorption at 2700-2800 cm^{-1} in IR spectra. The third isomer IIC (1.4 g, m.p. 100-102°$^+$) showed the NMR signals at 1.95 (OH singlet); 2.6 (C_6-H Wh=10); 2.95 (C_{10}-H Wh=20); 4.15 (C_4-H triplet J=5); 4.17 (C_2-H Wh=20); 7.31 (aromatic-H)$^{++}$; its acetate, 2.55 (C_6-H Wh=10); 2.8 (C_{10}-H Wh=20); 3.95 (C_4-H triplet J=5); 5.0 (C_2-H Wh=18); 7.1 ppm. (aromatic-H). The last isomer IID (2.6 g, m.p. 155-157°$^+$) showed the NMR signals at 2.15 (OH singlet); 2.67 (C_6-H Wh=10); 3.3 (C_{10}-H Wh=20); 3.95 (C_2-H Wh=30); 4.0 (C_4-H doublet-doublet J=3, 8); 7.31 (aromatic-H)$^{++}$; its acetate, 2.65 (C_6-H Wh=10); 3.2 (C_{10}-H Wh=20); 4.05 (C_4-H doublet-doublet J=3, 8); 4.9 (C_2-H multiplet); 7.23 ppm. (aromatic-H). A fraction contained the mixture of C and D isomers (ca. 3 g) was also obtained.

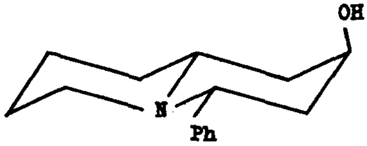
From the consideration of the NMR signals, it is suggested that the conformation of the isomer IIC is expressed as 2-hydroxy(a)-4-phenyl(e)-cis-quinolizidine, while the isomer IID is assigned 2-hydroxy(e)-4-phenyl(e)-cis-quinolizidine.



I



III



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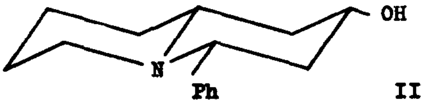

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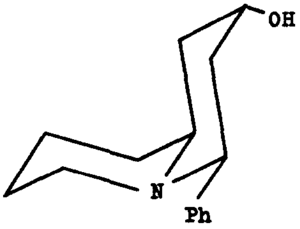
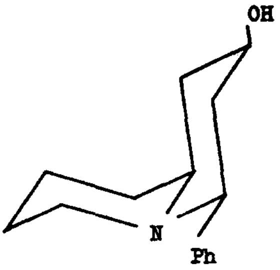


IIC



IID

\+ Satisfactory analyses were obtained with the compounds indicated by asterisks.

++ The NMR spectra indicated by double asterisks were measured in $CDCl_3$ solution and the other NMR spectra were measured in CCl_4 solution.

1) J. P. Ferris, C. B. Boyce and R. C. Bringer, Tetrahedron Letters 5129 (1966).

2) C. H. Tilford and M. G. v. Campen, J. Am. Chem. Soc. 76, 2431 (1954).

3) L. H. Goodson and H. Christopher, J. Am. Chem. Soc. 72, 358 (1950).

4) H. S. Aaron, G. E. Wicks and C. P. Rader, J. Org. Chem. 29, 2248 (1964).