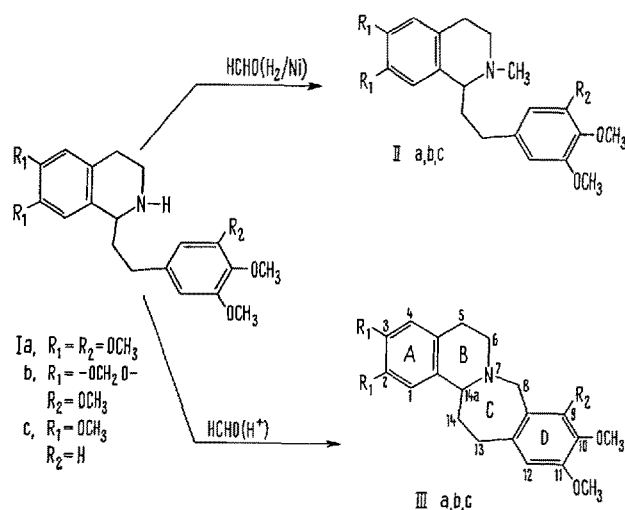


## (±)-Homoberbines, a New Class of Heterocyclic Compounds<sup>1</sup>

The recent isolation and structural elucidation of the alkaloids androcymbine<sup>2</sup>, melanthoidine<sup>3</sup>, and those belonging to the homoaporphine group<sup>4</sup>, clearly point to the existence of phenethylisoquinolines as precursors in the biogenetic process. Additionally, alkaloids derived from phenethylisoquinolines appear to follow biosynthetic pathways strongly reminiscent of those encountered in the benzylisoquinoline series.

In an effort to extend the locus of similarities between the phenethylisoquinolines and the benzylisoquinolines, we wish to report the preparation of a series of homoberbines III. These compounds are homologs of the tetrahydroprotoberberines (berbines). Homoberbines have not yet been found in nature, but they represent potential alkaloids which could be easily derived from *N*-methyl-tetrahydroisoquinolines of type II<sup>5</sup>.

For the preparation of the (±)-homoberbines IIIa and IIIb, the hydrochlorides of Ia and Ib<sup>5</sup> were condensed in a Pictet-Spengler type cyclization with excess 37% formaldehyde at 95°. The reaction mixture was then rendered alkaline and extracted with benzene. The benzene extract was filtered through an alumina column. Evaporation of the eluate gave a residue which was crystallized. The resulting tetracyclic compounds IIIa and IIIb were characterized as the free bases and the hydrochlorides.



The free base IIIa,  $\text{C}_{23}\text{H}_{29}\text{NO}_5$ , was recrystallized from ether, m.p. 148–150°;  $\lambda_{\text{sh}}^{\text{EtOH}}$  230 nm ( $\log \epsilon$  4.15) and  $\lambda_{\text{max}}^{\text{EtOH}}$  282 (3.62). The NMR-spectrum in  $\text{DMSO-d}_6$  exhibited peaks at 3.70, 3.73, 3.73, 3.77 and 3.77  $\delta$  ( $5\text{CH}_3\text{O}$ ); 3.82 and 4.36  $\delta$  (2H at  $\text{C}_8$ , 2 doublets,  $J_{\text{gem}}$  15 cps); aromatic singlets at 6.58, 6.62 and 6.67  $\delta$ . The hydrochloride crystallized from a mixture of ethanol-ether, m.p. 215–217°.

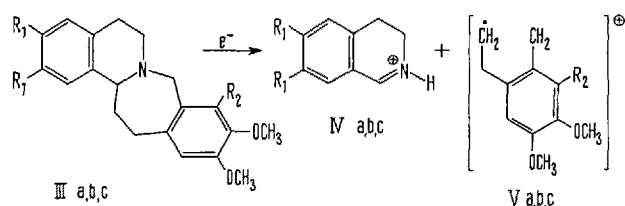
Free base IIIb,  $\text{C}_{22}\text{H}_{25}\text{NO}_5$ , was recrystallized from a mixture of ether-petroleum ether, m.p. 113–115°;  $\lambda_{\text{sh}}^{\text{EtOH}}$  230 nm ( $\log \epsilon$  4.13) and  $\lambda_{\text{max}}^{\text{EtOH}}$  289 (3.75). The NMR-spectrum in  $\text{DMSO-d}_6$  showed peaks at 3.72, 3.76 and 3.76  $\delta$  ( $3\text{CH}_3\text{O}$ ); 3.80 and 4.33  $\delta$  (2H at  $\text{C}_8$ , 2 doublets,  $J_{\text{gem}}$  15 cps); 5.88  $\delta$  ( $-\text{OCH}_2\text{O}-$  singlet); aromatic singlets at 6.52, 6.61 and 6.65  $\delta$ . The hydrochloride crystallized from a mixture of ethanol-ether, m.p. 241–243°.

In a separate series of experiments, the hydrochloride of Ic was refluxed with excess 37% formaldehyde. The reaction mixture was then made alkaline and extracted with chloroform. Preparative TLC resulted in the isola-

tion of 2 products, namely the *N*-methylphenethylisoquinoline IIc<sup>6</sup>, and the desired homoberbine IIIc.

Compound IIIc,  $\text{C}_{22}\text{H}_{27}\text{NO}_4$ , is a colorless oil with  $\lambda_{\text{max}}^{\text{EtOH}}$  210, 282 and 314 nm ( $\log \epsilon$  4.34, 3.75 and 3.13) and  $\lambda_{\text{sh}}^{\text{EtOH}}$  226 (4.20). The NMR-spectrum in  $\text{CDCl}_3$  exhibited absorptions at 3.83, 3.86, 3.88 and 3.88  $\delta$  ( $4\text{CH}_3\text{O}$ ); 4.00 and 4.45  $\delta$  (2H at  $\text{C}_8$ , 2 doublets,  $J_{\text{gem}}$  15 cps); aromatic singlets at 6.55, 6.57, 6.72 and 6.79  $\delta$ . Although the isoquinoline Ic can presumably condense with formaldehyde to form 2 homoberbines differing only in the position of the 2 methoxyl groups on ring D (i.e. 9, 10 or 10, 11), structure IIIc was assigned to the product by analogy with the protoberbine series<sup>7</sup> since vicinal coupling in the aromatic region of the NMR-spectrum was absent.

The mass spectra of the homoberbines show the expected molecular ion ( $M^+$ ) together with the ( $M-1$ )<sup>+</sup> peak. The main cleavage is along the lines indicated below, and in all cases the base peak corresponds to the ion V.



All compounds gave acceptable elemental analyses. The NMR-spectra were obtained on an A-60A Varian unit.

**Zusammenfassung.** Die sekundären Tetrahydroisoquinoline Ia, b, c wurden mit Hilfe einer modifizierten Pictet-Spengler-Kondensation in die (±)-Homoberbine IIIa, b, c übergeführt. Diese Homoberbine stellen eine neue Klasse potentieller Alkaloide dar.

A. BROSSI, A. I. RACHLIN,  
 S. TEITEL, M. SHAMMA  
 and M. J. HILLMAN<sup>8</sup>

Chemical Research Department, Hoffmann-La Roche Inc.,  
 Nutley (New Jersey 07110) and Department of  
 Chemistry, The Pennsylvania State  
 University, University Park  
 (Pennsylvania 16802, USA),  
 3 May 1968.

<sup>1</sup> Our proposed nomenclature for this ring system is: 5,6,8,13,14,14a-hexahydroisoquinolo[2,1-b][2]benzazepine.

<sup>2</sup> A. R. BATTERSBY, R. B. HERBERT, L. PIJEWSKA and F. ŠANTAVÝ, Chem. Commun. 228 (1965).

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<sup>4</sup> A. R. BATTERSBY, R. B. BRADBURY, R. B. HERBERT, M. H. G. MUNRO and R. RAMAGE, Chem. Commun. 450 (1967); T. KAMEYAMA, K. FUKUMOTO, H. YAGI and F. SATOH, Chem. Commun. 878 (1967).

<sup>5</sup> The synthesis of the secondary tetrahydroisoquinolines I and the corresponding tertiary amines II, which were needed also for other projects, will be reported by the 2 groups in separate papers.

<sup>6</sup> A. BROSSI, H. BESENDORF, B. PELLMONT, M. WALTER and O. SCHNIDER, Helv. Chim. Acta 43, 1459 (1960).

<sup>7</sup> R. H. F. MANSKE, in *The Alkaloids* (Ed. R. H. F. MANSKE; Academic Press, New York, N.Y. 1954), vol. 4, p. 78.

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