EXPERIENTIA

Vol. XIX – Fasc. 1 Pag. 1–56 15. I. 1963

Brèves communications – Kurze Mitteilungen – Brevi comunicazioni – Brief Reports

The Structures of Laurelliptine, a New Aporphine Alkaloid, and Thalicmidine

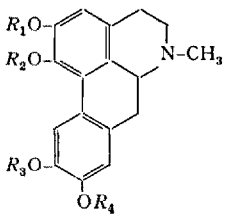
A new alkaloid, for which the name laurelliptine is proposed, has been isolated from *Beilschmiedia elliptica* White and Francis, an Australian member of the family Lauraceae. Laurelliptine [($C_{18}H_{19}NO_4$; m.p. 191°; $[\alpha]_D^{21}$ = +47° (ethanol)] contains two methoxyl groups and no methylimino groups and its ultraviolet absorption spectrum [λ_{max}^{EtOH} mμ (log ε): 280 (3.70), 305 (3.76)] is characteristic of an aporphine alkaloid. Upon treatment with diazomethane laurelliptine yields O,O-dimethyllaurelliptine (picrate, m. p. 135–137°) whilst with acetic anhydride the neutral O,O,N-triacetyllaurelliptine [m.p. 188–189°; $[\alpha]_D^{17}$ = + 76° (ethanol)] is formed. N-Methyllaurelliptine [m.p. 121–123°; $[\alpha]_D^{16}$ + 41° (ethanol)] is obtained when the natural base, together with formaldehyde, is hydrogenated over Raney Nickel. This establishes laurelliptine as a dimethoxy-diphenolic-noraporphine alkaloid.

Treatment of N-methyllaurelliptine with diazomethane yields two products one of which is still phenolic. The non-phenolic product, O,O,N-trimethyllaurelliptine has been shown to be identical (mixed m.p.; infra-red spectra, paper chromatography) with glaucine (Ia)[1] by direct comparison of the bases and their methiodides. The phenolic base O,N-dimethyllaurelliptine [m.p. 189–191°; $[\alpha]_D^{17}$ = +43° (ethanol)] gives a methiodide [m.p. 231–233°; $[\alpha]_D^{22}$ = + 26° (water)] the physical constants of which closely resemble those of the iodide [m.p. 226–229°; $[\alpha]_D$ = + 24°[2] (water)] of the quaternary aporphine base (II) isolated by RIGGS et al.[3] from *Fagara tinguassoiba*. The picrate of the N-methylaporphinium ion (m.p. 141–148°) obtained from N,O-dimethyllaurelliptine does not depress the m.p. of the picrate of (II) (m.p. 144–150°) and furthermore the infra-red spectra of the two picrates are identical.

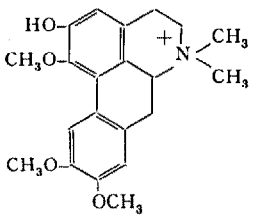
This establishes the position of one of the hydroxyl groups in N-methyllaurelliptine and the structure of this base must be (Ib), (Ic), or (Id).

(Ib) is boldine (m.p. 160–161°; $[\alpha]_D$ = + 128°)[4] which is not identical with N-methyllaurelliptine while (Ic) has been obtained by the hydrolysis of dicentrine (Ie) with dilute sulphuric acid in the presence of phloroglucinol[5]. Although this latter diphenolic aporphine has not been very well characterized (m.p. 175°d., with sintering from 140°) its melting point is sufficiently different from N-methyllaurelliptine for the two not to be identical. In agreement with this, laurelliptine does not give a Quastel Test[6] for a 1,2-dihydric phenol, and in addition, has the same Rf value on plain and boric acid/sodium acetate treated paper[7]. This argues against an *ortho* dihydroxyl grouping being present in this molecule. Hence we propose formula (Id) for N-methyllaurelliptine and (III) for laurelliptine itself.

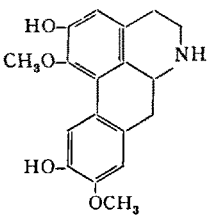
Recently SHAMMA[8] has reported a relationship between ring substituents and absolute configuration in the aporphine series. He has proposed that regardless of the nature of ring A certain substituents at particular positions of ring D can be associated with a specific absolute configuration of the aporphine alkaloid. Moreover it has



I



II



III

(a) $R_1 = R_2 = R_3 = R_4 = CH_3$
(b) $R_1 = R_4 = H$; $R_2 = R_3 = CH_3$
(c) $R_1 = R_2 = H$; $R_3 = R_4 = CH_3$
(d) $R_1 = R_3 = H$; $R_2 = R_4 = CH_3$
(e) $R_1 — R_2 = -CH_2-$; $R_3 = R_4 = CH_3$
(f) $R_1 — R_2 = -CH_2-$; $R_3 = H$ $R_4 = CH_3$
(g) $R_1 = R_2 = R_4 = CH_3$; $R_3 = H$
(h) $R_1 = R_2 = R_3 = CH_3$; $R_4 = H$
(i) $R_1 = R_3 = R_4 = CH_3$; $R_2 = H$
(k) $R_1 = H$; $R_2 = R_3 = R_4 = CH_3$

[1] Numbering system as recommended by A. M. PATTERSON, L. T. CAPELL, and D. F. WALKER, *The Ring Index* (American Chemical Society, Washington D.C. 1959), p. 704, Serial Number 5171.
[2] Calculated from the value given by MARION[3] for the chloride salt.
[3] N. V. RIGGS, L. ANTONACCIO, and L. MARION, Can. J. Chem. *39*, 1330 (1961).
[4] T. NAKASATO and S. NOMURA, Bull. pharm. Soc. Japan *7*, 780 (1959).
[5] S. OSADA, J. pharm. Soc. Japan *48*, 423 (1928); Chem. Abstr. *22*, 3664 (1928).
[6] J. H. QUASTEL, Analyst *56*, 311 (1931).
[7] L. JURD, J. Chromatography *4*, 369 (1960).
[8] M. SHAMMA, Exper. *17*, 64 (1962).

been suggested[9-11] that the sign of the specific rotation of the aporphine alkaloids at 589 mμ is a true criterion of their absolute configuration. On the basis of these correlations one would expect that phanostenine (If)[12] laurelliptine, and N-methyllaurelliptine with the same 9-methoxy-10-hydroxy substitution pattern in ring D would have the same sign of rotation. This is not so. Laurelliptine and N-methyllaurelliptine are dextrorotatory while phanostenine is levorotatory. Hence we must conclude that we have an exception to one of these correlations.

On the basis of this proposed relationship between substituents and absolute configuration SHAMMA[8] has suggested that thalicmidine[13], a levorotatory, monophenolic alkaloid of the glaucine series has structure (Ig). Although the validity of this relationship is perhaps questionable the results published in this communication prove that the above structure for thalicmidine is correct. Of the four possible structures for a mono-O-des-methylglaucine three have now been reported. (Ih) is N-methyllaurotetanine, (Ii) is glaucentrine and (Ik) is N,O-dimethyllaurelliptine. As the properties of these bases do not correspond with those of thalicmidine, the structure of this latter base, by exclusion must be (Ig).

Experiments are in hand to synthesise laurelliptine and thalicmidine[14].

Zusammenfassung. Dem neuen aus *Beilschmiedia elliptica* isolierten Alkaloid Laurelliptin wurde die Struktur 1,9-Dimethoxy-2,10-dihydroxy-noraporphin (III) zugeschrieben. Die früher (von SHAMMA) vorgeschlagene Struktur für Thalicmidin (Ig) wurde bestätigt.

P. S. CLEZY, A. W. NICHOL, and E. GELLERT

Department of Organic Chemistry, University of New South Wales, Sydney (Australia), and Wollongong University College, Wollongong (N.S.W. Australia), July 30, 1962.

[9] K. W. BENTLEY and H. M. E. CARDWELL, J. chem. Soc. *1955*, 3252.
[10] M. SHAMMA, Exper. *16*, 484 (1960).
[11] C. DJERASSI, K. MISLOW, and M. SHAMMA, Exper. *18*, 53 (1961).
[12] M. TOMITA and I. KIKKAWA, Yakugaku Zasshi *77*, 1011 (1957); Chem. Abstr. *52*, 3833c (1958).
[13] S. YUNUSOV and N. N. PROGRESSOV, Zhur. Obshchei Khim. *20*, 1151 (1950); Chem. Abstr. *45*, 1608c (1951); Zhur. Obshchei Khim. *22*, 1047 (1952); Chem. Abstr. *48*, 2731c (1954).
[14] We are grateful to the Phytochemical Survey Unit of the Division of Organic Chemistry, C.S.I.R.O. for the collection of material, to Dr. MANSKE for samples of glaucine and its methiodide and to Dr. MARION for the picrate of compound (II).

Steroid Hormones and Monolayers

In a recent review[1], WILLMER proposed a model to explain the manifold physiological effects of steroid hormones. One of its salient features involves the interaction between these hormones and lipids of the cell membrane; only those steroids which have the 'flat' shape similar to cholesterol are said to penetrate the lipids of the membrane, and consequently are active as hormones. The attractiveness of this idea prompted us to determine whether steroid hormones indeed penetrate into monomolecular lipid films and remain there. Clearly, demonstration of such interactions with simple models, would lend considerable support to WILLMER's theory.

A Langmuir-type film balance was used to obtain surface pressure ($\pm$ 0.05 dynes/cm)-area data; simultaneously, surface potentials ($\pm$ 10 mV) were measured using a Ra^{226} electrode and an electrometer. In all cases, benzene-alcohol (20:1) was used as the spreading solvent for the monolayers. Three types of films were prepared: (a) hormonally active and inactive steroids were spread as monolayers on water (pH6 and pH2) to determine their orientation at the air/water interface; (b) equimolar mixtures of representative steroids with cholesterol or cholesterol-stearic acid (1:3) were spread on water; and (c) monolayers of stearic acid, cholesterol or cholesterol-stearic acid (1:3) were spread on the surface of a saturated aqueous solution of cortisol.

In the first series (a), results obtained with estrone, androsterone, and etiocholanolone indicated that the steroids form gaseous monolayers without reorienting to a vertical position. Collapse pressures were less than 0.5 dynes/cm for each compound; surface potentials were + 10, + 40, and + 35 mV, respectively; surface pressures and potentials were stable.

In the second series (b), the addition of androsterone, etiocholanolone, and progesterone had no effect on either the surface pressure or the potential of the monolayers of cholesterol, or cholesterol-stearic acid.

In the last series (c), cortisol had very little effect on the surface pressure–area relations for the three monolayers (stearic acid, cholesterol, or stearic acid-cholesterol (3:1)); above 3 dynes/cm all three surface pressure–area curves coincided with those of the hormone-free systems. The surface potential in each case was reduced by $\sim$ 150 mV from the values observed for the hormone-free system.

If film penetration by the steroids had occurred, one would expect to find more pronounced effects than those observed. Even carcinogens which do not form films show fairly strong interactions with stearic acid and cholesterol monolayers[2]. Our results do not support the mechanism proposed by WILLMER, but indicate non-specific adsorption of steroid hormones at the monolayer/water interface, rather than film penetration. MUNCK[3] also found steroids to orient horizontally at the heptane/water interface, in agreement with our findings.

Zusammenfassung. Der Einfluss verschiedener Vertreter der Steroidhormone auf die Eigenschaften monomolekularer Filme von Cholesterin und Stearinsäure wurde mittels der Langmuir–Waage geprüft. Es konnte kein Eindringen der Steroide in die Filme festgestellt werden, sodass die Vorstellungen von Willmer über die Wirkungsweise der Steroidhormone experimentell nicht zu stützen waren.

N. L. GERSHFELD and E. HEFTMANN

National Institutes of Health, National Institute of Arthritis and Metabolic Diseases, Bethesda (Maryland, U.S.A.), September 24, 1962.

[1] E. N. WILLMER, Biol. Rev. *36*, 368 (1961).
[2] W. W. DAVIS, M. E. KRAHL, and G. H. A. CLOWES, J. Amer. chem. Soc. *62*, 3080 (1940).
[3] A. MUNCK, Biochim. biophys. Acta *24*, 507 (1957).