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THE STRUCTURE OF JULOCROTINE

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ANASTASI[1] has reported the isolation of an alkaloid "julocrotine" from Julocroton montevidensis (fam. Euphorbiaceae), but except for the observation that it gives the usual alkaloid reactions, is labile to acid or alkali, melts at 105° and corresponds to the empirical formula $C_{19}H_{26}N_2O_3$, no further information has been published on this substance. We should now like to report certain experiments which demonstrate that julocrotine possesses structure I.

In our hands, julocrotine exhibited m.p. 108-109°, $[\alpha]_D$ -9° (chloroform), -50° (methanol) and its empirical formula corresponded to $C_{18}H_{24}N_2O_3$

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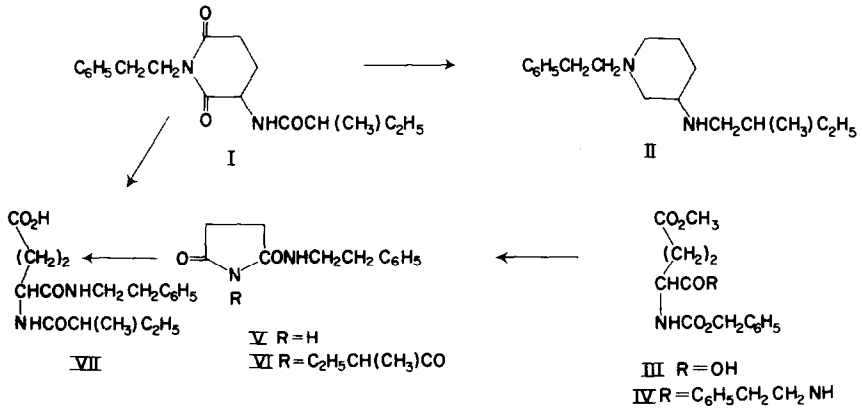
[1] C. Anastasi, Anal. Asoc. Quim. Argentina 13, 348 (1925). Subsequently the substance was also isolated from J. subpannosus and J. camporum (unpublished results of A. Novelli cited by A. Novelli and O. O. Orazi, Rev. Farmaceutica (Buenos Aires) 92, 102 (1950)).

(Calc.: C, 68.33; H, 7.65; N, 8.85; O, 15.17; C-CH_3, 4.75; mol. wt., 316. Found: C, 68.09; H, 7.72; N, 9.03; O, 15.41; OCH_3, 0.0; C-CH_3, 6.11; M (Rast), 309). In the strict sense of the word, julocrotine is not an alkaloid since it does not possess any titratable basic nitrogen. Its ultraviolet absorption spectrum is typical of an isolated benzene ring, while its infrared spectrum (chloroform) exhibited bands at 2.93 (sharp), 5.76 (w), 5.93 (s) and 6.65 (s) μ. Perhydrogenation with platinum oxide in acetic acid resulted in the uptake of three molar equivalents of hydrogen and the formation of hexahydrojulocrotine ($C_{18}H_{30}N_2O_3$, m.p. 93-94°), which does not anymore show the typical ultraviolet benzenoid absorption.



Reduction of julocrotine with lithium aluminum hydride caused the loss of all oxygen functions and yielded an oily base ($[\alpha]_D$ -12.6° (chloroform); Calc. for $C_{18}H_{30}N_2$: C, 78.77; H, 11.02; N, 10.21; C-CH_3, 5.48. Found: C, 78.10; H, 10.92; N, 9.84; C-CH_3, 8.10), subsequently shown to be II. In contrast to the non-basic starting material julocrotine, the lithium

aluminum hydride reduction product formed a dipicrate (m.p. 186-187°) and a dimethiodide (m.p. 226-227°) thus suggesting that the three oxygen atoms of julocrotine are present in the form of an amide and an imide function. Hydrogenation of the liquied base again resulted in the uptake of three molar equivalents of hydrogen and the disappearance of the benzenoid absorption spectrum, implying that julocrotine must contain one additional ring aside from a benzene nucleus. Hofmann degradation of the dimethiodide of m.p. 226-227° yielded an optically active diamine (to be described in our detailed publication) and a neutral oil, which furnished benzoic acid upon permanganate oxidation. Further information about the benzene fragment was provided by the alkaline hydrolysis of julocrotine, from which β-phenylethylamine could be isolated. In addition, there were isolated two isomeric acids (corresponding to $C_{18}H_{26}N_2O_4$) containing no basic nitrogen and these are referred to as julocrotic acid-A (m.p. 119-122°, $[\alpha]_D$ +14° (methanol); methyl ester $C_{19}H_{28}N_2O_4$, m.p. 148-149°) and julocrotic acid-B (m.p. 133.5-135°). These results are best interpreted by assuming alternate hydrolytic opening of an unsymmetrical cyclic imide.

Comparison of the infrared carbonyl bands of julocrotine ($\lambda_{max}^{CHCl_3}$ 5.76 (w) and 5.93 (s) μ) with those of N-β-phenylethylsuccinimide ($\lambda_{max}^{CHCl_3}$ 5.63 (w) and 5.85 (s) μ) and N-β-phenylethylglutarimide ($\lambda_{max}^{CHCl_3}$ 5.78 (w) and 5.96 (s) μ) demonstrates clearly[2] that julocrotine is a glutarimide derivative. This was established by the course of the acid hydrolysis (dioxanehydrochloric acid, 24 hr refluxing) which furnished β-phenyl-

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[2] Infrared bands for other substituted succinimides and glutarimides are given by H. K. Hall and R. Zbinden, J. Amer. Chem. Soc. 80, 6428 (1958) and by V. M. Clark, A. W. Johnson, I. O. Sutherland and A. Todd, J. Chem. Soc. 3283 (1958).

ethylamine, L-(+)-glutamic acid and (+)-α-methylbutyric acid [p-bromoanilide, m.p. 135-136°, $[\alpha]_D$ +31.3° (acetone); anilide, m.p. 96-97°, $[\alpha]_D$ +40.2° (acetone)], all of which can be accommodated in expression I for julocrotine.

Verification of this structure was provided by the synthesis of julocrotic acid-A (VII) according to the following scheme. γ-Methyl N-carbobenzyloxy-L-glutamate (III)[3] was converted to the acid chloride with phosphorus pentachloride in ether solution and treated directly with β-phenylethylamine to afford the amide IV (m.p. 124-125°, $[\alpha]_D$ -8.6° (chloroform), $\lambda_{max}^{CHCl_3}$ 2.92, 5.75 and 5.93 μ; Calc. for $C_{22}H_{26}N_2O_5$: C, 66.31; H, 6.58; N, 7.03; O, 20.08. Found: C, 66.15; H, 6.36; N, 7.29; O, 20.11). Hydrogenolysis with palladium black in aqueous methanol containing some acetic acid, evaporation to dryness and recrystallization from ether gave the β-phenylethylamide of 2-keto-pyrrolidine-5-carboxylic acid (V) (m.p. 140-142°, $[\alpha]_D$ -47° (chloroform); Calc. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06; O, 13.78. Found: C, 66.84; H, 6.86; N, 11.98; O, 14.03; OCH_3, 0.0), identical with a specimen derived from successive treatment of 2-ketopyrrolidine-5-carboxylic acid[4] with thionyl chloride and then with β-phenylamine. Treatment of V with (+)-α-methylbutyryl chloride in pyridine solution led to N-(α-methylbutyryl)-2-ketopyrrolidine-5-carboxylic acid β-phenylethylamide (VI) (m.p. 102-104°, $[\alpha]_D$ -24° (methanol); Calc. for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.12; H, 7.45; N, 8.92), which was hydrolyzed[5] with 5% methanolic

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[3] W. E. Hanby, S. G. Waley and J. Watson, J. Chem. Soc. 3239 (1958).
[4] E. Abderhalden and K. Kautzsch, Z. Physiol. Chem. 68, 487 (1910).
[5] See A. R. Battersby and J. C. Robinson, J. Chem. Soc. 2076 (1956).

potassium hydroxide to julocrotic acid-A (VII). Identity with a specimen derived from julocrotine (I) was established by coincidence of the melting points, optical rotations and infrared spectra of the appropriate acids and methyl esters.

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