NOTES

in toluene, except 19 and 20, which, due to limited solubility, were measured as saturated solutions. All values are relative to 2,5-diphenyloxazole which is assigned the arbitrary value of 1.00.

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# The Constituents of *Casimiroa Edulis* Llave et Lex. IV.<sup>1</sup> Identification of Edulein with 7-Methoxy-1-methyl-2-phenyl-4-quinolone

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The isolation of the three new alkaloids edulein, edulitine, and edulinine from the bark of the tree *Casimiroa edulis* Llave *et* Lex, was reported in a previous paper of this series.<sup>2</sup> We now describe the elucidation of the structure of edulein through its identification with an alkaloid of known structure which was reported since our original paper was written.

Edulein, C<sub>17</sub>H<sub>15</sub>NO<sub>2</sub>, m.p. 201°, was previously shown to contain one methoxyl and one N-methyl group.<sup>2</sup> It was suggested that edule in contained an amide grouping since it was essentially neutral and the amide must have been tertiary in view of the absence of active hydrogen. Boiling edulein with potassium hydroxide in ethylene glycol has now given demethyledulein, C<sub>16</sub>H<sub>13</sub>NO<sub>2</sub>, m.p. 324°, which no longer contains the methoxyl function. The substance is derived from edule in by cleavage of the methoxyl group to hydroxyl since methylation with diazomethane regenerated edulein. Boiling edulein with hydriodic acid likewise yielded demethyledulein and the alkaloid, like casimiroin,  $^{1}$  is therefore very stable under both acidic and basic conditions.

The reduction of edulein with lithium aluminum hydride gave dihydroedulein,  $C_{17}H_{17}NO_2$ , m.p.

130°. The formation of this substance made the presence of an amide in edulein unlikely, since amides are generally reduced to the amines (involving loss of an oxygen atom) with lithium aluminum hydride.<sup>3</sup> The presence of a vinylogous tertiary amide of type I in edulein was indicated, since this would still account for the essentially non-basic character of the alkaloid and also for its reduction to a dihydro derivative. Such a formulation moreover lacks only a phenyl group to make up the complete structure of edulein.



At this stage of the investigation we were made aware through an interesting discussion with Dr. Sidney Goodwin (National Heart Institute, National Institutes of Health, Bethesda, Md.) of the similarity between edulein and an alkaloid isolated from the bark of Lunasia amara by Dr. J. R. Price et al. (Commonwealth Scientific and Industrial Research Organization, Melbourne, Australia) and from the leaves by Dr. Goodwin et al. This alkaloid, which has been found to be 7-methoxy-1methyl-2-phenyl-4-quinolone (IIa),<sup>4</sup> was shown by us by direct comparison to be completely identical with edulein. A difference seemed to lie in the picrates, since edulein picrate has been reported to have m.p. 192°<sup>2</sup> whereas the picrate of IIa has m.p. 220°.5 The lower melting point of edulein picrate must have been due to polymorphism, since a new preparation showed the same melting point as the picrate of IIa and there was no depression on admixture. Edulein is therefore 7-methoxy-1-methyl-2-phenyl-4-quinoline (IIa) and demethyledulein is 7-hydroxy-1-methyl-2-phenyl-4-quinolone (IIb).

Dihydroedulein is comparatively non-polar, is not extracted from ether solution with mineral acids, and shows strong carbonyl absorption in the infrared ( $\lambda_{max}$  6.01, 6.20, and 6.37  $\mu$ ). It is most probably 7-methoxy-1-methyl-2-phenyl-4-keto-1,-2,3,4-tetrahydroquinoline (III), derived from edu-

<sup>(1)</sup> Part III, A. Meisels and F. Sondheimer, J. Am. Chem. Soc., 79, 6328 (1957).

<sup>(2)</sup> J. Iriarte, F. A. Kinel, G. Rosenkranz, and F. Sondheimer, J. Chem. Soc., 4170 (1956).

<sup>(3)</sup> Cf. W. G. Brown, Org. Reactions, Vol. 6, Chapter 10, pp. 479-480 (1951); N. G. Gaylord, Reduction with Complex Metal Hydrides, Interscience Publishers Inc., New York, 1956, pp. 544-592.

<sup>(4)</sup> J. R. Price, Fortschr. Chem. org. Naturstoffe, 13, 310 (1956).

<sup>(5)</sup> J. R. Price, private communication.

lein (IIa) by 1,4-addition of hydrogen. This structure, which still represents a vinylogous amide, accounts for the non-basic properties of the reduced substance. Support for the correctness of this formulation is provided by the similarity of the infrared spectrum of dihvdroedulein in the carbonyl region with that of the similarly constituted 1methyl-4-keto-7,8-methylenedioxy-1,2,3,4-tetrahydroquinoline (IV) ( $\lambda_{max}$  5.99, 6.17, and 6.34  $\mu$ ), the lithium aluminum hydride reduction product of casimiroin.<sup>1</sup>

#### EXPERIMENTAL<sup>6</sup>

Demethyledulein (7-hydroxy-1-methyl-2-phenyl-4-quinolone) (IIb). A mixture of 90 mg. of edulein, 1 g. of potassium hydroxide, and 10 cc. of ethylene glycol was boiled under reflux for 24 hr. Water was added, the solution was filtered, the filtrate was acidified with dilute hydrochloric acid, and the precipitate was collected. Crystallization from ethanol gave 74 mg. of demethyledulein as needles, m.p. 322-324° (dec.). The substance gave a red color with alcoholic ferric chloride.

Anal. Caled. for C<sub>16</sub>H<sub>13</sub>NO<sub>2</sub>: C, 76.47; H, 5.22. Found: C, 76.25; H, 5.36.

The same substance was obtained by boiling edulein (90 mg.) with hydriodic acid (3 cc.; d 1.7) for 1 hr.

Treatment of demethyledulein in ether suspension with ethereal diazomethane at 5° for 24 hr. regenerated edulein in almost quantitative yield.

Dihydroedulein (7-methoxy-1-methyl-2-phenyl-4-keto-1,2,3,-4-tetrahydroquinoline (III). Edulein (150 mg.) dissolved in 25 cc. of dry tetrahydrofuran was added dropwise to a solution of 500 mg. of lithium aluminum hydride in 15 cc. of tetrahydrofuran and the mixture was boiled under reflux for 7 hr. It was then cooled, poured into ice cold dilute sulfuric acid, and extracted with ether. The ethereal extract was washed with water, dried, and evaporated. Chromatography of the residue on 3.5 g. of alumina and crystallization of the fractions eluted with pentane-benzene (1:1) from etherpentane gave 105 mg. of dihydroedulein, m.p. 129-130°,  $\lambda_{\text{max}}$  238, 255, 283, and 375 m $\mu$  (log  $\epsilon$  4.21, 4.37, 3.96, and 3.70, respectively),  $\lambda_{\text{max}}$  6.01, 6.20 and 6.37  $\mu$ , no hydroxyl band.

Anal. Calcd. for C17H17NO2: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.18; H, 6.19; N, 5.25.

Identification of edulein with 7-methoxy-1-methyl-2-phenyl-4-quinoline (IIa). A sample of edulein, m.p. 200-201°, gave no melting point depression on admixture with a sample of IIa (m.p. 199-200°) obtained by Dr. J. R. Price from the bark of Lunasia amara. The infrared spectrum of edulein was re-determined ( $\lambda_{max}$ . 6.15, 6.19, 6.24, 6.33, and 6.39  $\mu$ ) and was found to be completely identical with the spectrum of IIa.

Edulein picrate was prepared again and after crystallization from methanol formed yellow needles, m.p. 220-221°. There was no depression on admixture with a sample of the picrate of IIa, m.p. 220-221°, kindly supplied by Dr. Price.

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# **Spiroisoindolinium Salts**

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During an investigation of various types of quaternary ammonium salts, seven new spiroisoindolinium compounds were prepared for pharmacological evaluation (Table I). These derivatives resulted from the reaction of cyclic secondary amines and various o-xylvlene halides in the manner generally described by other investi-gators.<sup>2-5</sup> While most of the intermediates used have been previously described, improved preparations of some of them are reported in the experimental part.

The isoindolinium salts were pressor agents in dogs. No other marked pharmacological activity was noted.

# EXPERIMENTAL<sup>6</sup>

General procedure. The isoindolinium salts were prepared by heating under reflux a mixture of 0.1 mole of an o-xylylene halide and 0.1 mole of a cyclic secondary amine in 600 ml. of isopropyl alcohol containing 0.1 mole of sodium hydroxide and 10 ml. of water. After 6 to 18 hr. the solution was filtered, then concentrated to a volume of 50 to 150 ml. and filtered again to remove inorganic material. The product was obtained by diluting the filtrate with anhydrous ether and refrigerating the mixture.

Crude yields of 60 to 90% were obtained. The products were recrystallized and dried in vacuo before analysis.

Secondary amines. Hexamethyleneimine was obtained from a commercial source; 2- and 4-methyl hexamethyleneimine were prepared by the method of Blicke and Doorenbos.<sup>7</sup>

Intermediates. 1,2-Bis( $\alpha$ -bromoethyl)benzene. A mixture of 5.0 g. (0.03 mole) of 1,2-bis( $\alpha$ -hydroxyethyl) benzene<sup>8</sup> and 100 ml. of 65% aqueous hydrobromic acid was stirred for 48 hr. at room temperature, then poured into a mixture of 250 g. of ice and 250 ml. of water. The solid was separated by filtration, washed well with water and air-dried to give 8.4 g. (96%) of pure product, m.p. 88-91°.

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(2) M. Scholtz, Ber., 31, 414 (1898).

(3) J. von Braun, Ber., 49, 2640 (1916).
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(5) F. F. Blicke and E. B. Hotelling, J. Am. Chem. Soc., 76, 5099 (1954).

(6) All melting and boiling points as uncorrected.

(7) F. F. Blicke and N. J. Doorenbos, J. Am. Chem. Soc., 76, 2317 (1954).

(8) M. Deluchat, Compt. rend., 190, 438 (1930).

(9) M. Deluchat, Compt. rend., 192, 1387 (1931), m.p. 91°

<sup>(6)</sup> Melting points are uncorrected. The ultraviolet spectrum was measured in 95% ethanol solution on a Unicam Model S.P. 500 spectrophotometer and the infrared spectra in chloroform solution on a Baird double-beam recording spectrophotometer. The analyses were carried out in our microanalytical department under the direction of Mr. Erich Meier.