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THE STRUCTURE AND SYNTHESIS OF LIRIODENINE, A NEW TYPE OF ISOQUINOLINE ALKALOID

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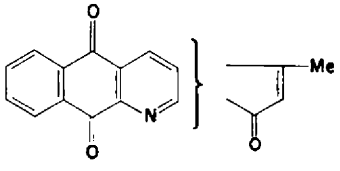
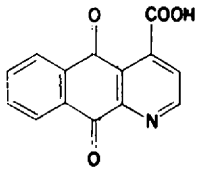
Abstract—Liriodenine (III) is recognised to be a representative of a new class of isoquinoline alkaloid belonging to the aporphine subgroup. A synthetic procedure for this type of alkaloid is developed and applied to the specific case of liriodenine, the key step being the Pschorr cyclization of 1-2′-aminobenzoyl-6,7-methylenedioxyisoquinoline.

THE tulip tree (*Liriodendron tulipifera* L.) is widely distributed throughout the eastern part of the United States. It finds use as an ornamental tree, and also because of the yellow color of the heartwood is useful for lumber. This color is to its disadvantage however for the groundwood pulp prepared from the wood. The source of this yellow color has been traced[1] to at least two alkaloids. One of them, liriodenine, $C_{17}H_9O_3N$, was examined in detail and evidence was presented in support of the structure I. The presence of three of the rings in liriodenine was considered to have been established by its oxidation to a benzo[g]quinoline-5,10-dione carboxylic acid which is, in our opinion, II (see below). Upon heating it decarboxylated to furnish the known aza-anthraquinone (II; COOH=H). The nature of the remaining ring was not determined but was inferred from the formation of an oxime, the suggested presence of a methyl group (I.R.), and the lack of a hydroxyl, methylenedioxy or methoxyl in the alkaloid.

Buchanan and Dickey recognized, in proposing the structure I for liriodenine, that it was a very unusual one for a natural product. In fact only one other case was quoted, *viz.* phomazarine[2] isolated from the mould, *Phoma terrestris*. In this connection a recent attempt[3] to reisolate this pigment led not to phomazarine but to the polyhydroxyanthraquinone, cynodotin.



I



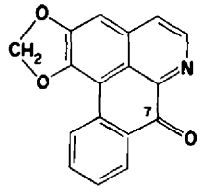
II

We felt that the published evidence for the structure of liriodenine could be interpreted differently. On the basis of formula I for the alkaloid, it seemed strange that oxidation should have produced a monocarboxylic acid rather than a dicarboxylic

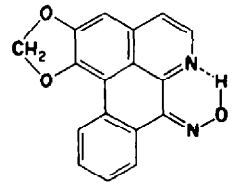
[1] M. A. Buchanan and E. E. Dickey, *J. Org. Chem.* **25**, 1389 (1960).
[2] F. Kögl and J. Sparenburg, *Rec. Trav. Chim.* **59**, 1180 (1940); F. Kögl and F. S. Quackenbush, *Ibid.* **63**, 251 (1944).
[3] D. E. Wright and K. Schofield, *Nature, Lond.* **188**, 233 (1960).

one. However if it is assumed that the quinone moiety does not preexist in liriodenine but is generated along with the carboxyl during the oxidation, then we would have an alternative explanation for the experimental results. The infrared spectrum of liriodenine as compared with benzo[g]quinoline-5,10-dione was in agreement with this idea. The latter compound showed two carbonyl peaks whereas the alkaloid (supposed to have three carbonyl groups) had only one sharp peak. If liriodenine has only one carbonyl then two oxygen functions have still to be accounted for, they cannot be either hydroxyl (no OH in the I.R.) or methoxyl (negative Zeisel). This leaves cyclic ethers as the only possibility and the simplest one which would account for both oxygens is a methylenedioxy group. Support for this hypothesis is to be found in the infrared spectrum[1] of the alkaloid which has bands at 1490, 1420, 1360, 1120, 1050 and 960 cm^{-1}, positions considered to be diagnostic[4] for the methylenedioxy group. With these ideas in mind, and remembering that the tulip tree is in the family Magnoliaceae from which up till now only benzylisoquinoline type bases have been isolated, we arrive at a new possible structure, 1,2-methylenedioxy-7-oxo-dibenzo-[de-g]quinoline(III)[5] for liriodenine.

On this basis then, liriodenine oxime (IV) should show neither hydroxyl nor carbonyl bands in the infrared. The special conditions for the formation of the acid (II),



III



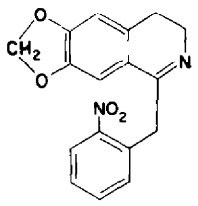
IV

which is known[6] and with which its properties are in good agreement, are now clear. Liriodenine is stated to give reactions characteristic of quinones. The structure III is consistent with these tests in as much as its reduction products would be expected to reoxidize very easily; compare, for example, the analogous case of perinaphthen-1-one.[7]

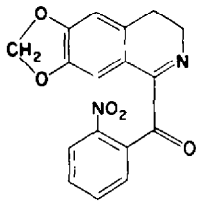
These conclusions received confirmation through a facile synthesis of liriodenine. The route took advantage of the knowledge which had been gained by earlier workers in the preparation of 1-benzoylisoquinolines from 1-benzyl-3,4-dihydroisoquinolines[8] as well as the results obtained from Pschorr cyclizations of 1-2′-aminobenzoyltetrahydroisoquinolines.[9] Thus 1-2′-nitrobenzyl-6,7-methylenedioxy-3,4-dihydroisoquinoline[10] (V) upon oxidation with chromic oxide in acetic acid gave the benzoyl derivative (VI) which in hot alcoholic alkali furnished the desired 1-2′-nitrobenzoyl-6,7-methylenedioxyisoquinoline (VII). Reduction of this compound, diazotization and

[4] L. H. Briggs, L. D. Colebrook, H. M. Fales and W. C. Wildman, *Analyt. Chem.* **29**, 904 (1957).
[5] The unsubstituted heterocycle is known, British Patent 450,244 [*Chem. Abstr.* **30**, 8638 (1936)] but no physical properties are given and the synthetic route, ring closure of 1-benzoylisoquinoline with aluminium chloride, is not applicable to a synthesis of liriodenine.
[6] A. Etienne and A. Staehelin, *Bull. Soc. Chim. Fr.* 748 (1954).
[7] E. Clar, *Aromatische Kohlenwasserstoffe* (2nd. Ed.). Springer, Berlin (1952).
[8] *Inter alia*, J. S. Buck, R. D. Haworth and W. H. Perkin, Jr., *J. Chem. Soc.* **125**, 2176 (1924).
[9] E. Schlittler and A. Lindenmann, *Helv. Chim. Acta* **32**, 1880 (1949).
[10] G. Barger and G. Weitnauer, *Helv. Chim. Acta* **22**, 1036 (1939).

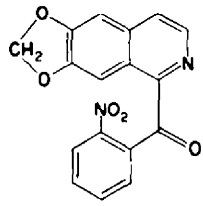
heating to effect the Pschorr cyclization gave directly a product indistinguishable from liriodenine. This synthetic route should prove applicable to other members of this class of alkaloid. For example, Buchanan and Dickey[1] have isolated a second yellow alkaloid which was characterized but no formula was given. From the data



V



VI



VII

presented we believe that it may be a tetramethoxy analogue of liriodenine, perhaps 1,2,9,10- or 1,2,10,11-tetramethoxy-7-oxo-dibenzo[de,g]quinoline. This point is being investigated synthetically.

The yellow bases isolated from the tulip tree may be artefacts produced by aerial oxidation of (nor) aporphines but Buchanan and Dickey have not reported any other alkaloids from the heartwood. On the other hand these yellow bases may be widely distributed albeit in low yield and may have escaped detection until now because so much of the work on the isolation of isoquinoline alkaloids has been carried out before chromatographic methods became widely used.

The occurrence of liriodenine adds one more example to those alkaloids which exist in a higher oxidation state than required by the primary biogenetic process. The function, if any, of liriodenine in the plant is not known, but since it can theoretically accept one electron to form a stable anion radical, its participation in the biological transference of electrons, i.e. in oxidative and reductive processes, is a distinct possibility.

Note added in proof: We have now shown by a synthesis starting from papaverine that the second unnamed yellow alkaloid is 1,2,9,10-tetramethoxy-7-oxodibenzo [de,g]-quinoline and that the aporphine, d-glaucine, is the major alkaloid of the heartwood.

EXPERIMENTAL

1-2′-Nitrobenzoyl-6,7-methylenedioxy-3,4-dihydroisoquinoline (VI)

1-2′-nitrobenzyl-6,7-methylenedioxy-3,4-dihydroisoquinoline[10] (1 g) dissolved in acetic acid (10 ml) was warmed with chromic oxide (1 g) to 60° when a vigorous exothermic reaction set in. The temperature rose to 105° before subsiding. The reaction mixture was diluted with water and the resulting precipitate was extracted into methylenechloride which was then washed with alkali, dried and concentrated. Methanol was added and the remaining methylenechloride boiled off whereupon the product (VI), 450 mg, m.p. 180–183°, crystallized out. (Found: C, 62·8; H, 3·7. $C_{17}H_{12}O_5N_2$ requires: C, 63·0; H, 3·7%).

1-2′-Nitrobenzoyl-6,7-methylenedioxyisoquinoline (VII)

The above benzoylisoquinoline (250 mg) was dissolved in boiling ethanol to which several drops of 50% sodium hydroxide were added. The solution took on a purple color which gradually faded along with the appearance of a crystalline substance. After 10 min further heating the solution was allowed to cool and the pure benzoylisoquinoline (VII), 250 mg, m.p. 252° (decomp.) was filtered off. (Found: C, 63·0; H, 3·4. $C_{17}H_{10}O_5N_2$ requires: C, 63·4; H, 3·1%).

Liriodenine (III)

The above nitro compound (210 mg) was suspended in ethanol and shaken in an atmosphere of hydrogen, using a Raney nickel catalyst (ca. 500 mg) for 16 hr. After filtration, and concentration to dryness, the resulting solid (150 mg) was taken up into methanol (5 ml) and 2 N sulphuric acid (5 ml), cooled to zero degrees and diazotized (0·5 ml of N sodium nitrite were used). The reaction mixture was heated on a steambath for 30 min when it assumed a bright red color. Upon cooling, basifying and extraction into methylenechloride, there was obtained a yellow crystalline residue (100 mg) which gave directly from chloroform a product (40 mg), m.p. 289°, whose ultraviolet and infrared spectra were respectively identical with those recorded for liriodenine. (Found: C, 74·0; H, 3·3. $C_{17}H_9O_3N$ requires: C, 74·2; H, 3·3%).

Acknowledgement—We are indebted to Dr. E. Schlittler for many interesting discussions during the development of this work.