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# THE STRUCTURE OF LUNARINE[1]

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Lunarine, ($C_{25}H_{31}N_3O_4$) the chief alkaloid of *Lunaria biennis*,[4-7] and of *Lunaria rediviva*,[9] is a monoacid base containing one ketonic carbonyl group, one benzene ring, and two ethylenic double bonds in the molecule.[8,10]

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[1] This is the 6th paper in the series 'Alcaloides du lunaria biennis Moench' (Paris) and the 4th in the series 'The Chemistry of Lunaria Alkaloids' (Glasgow).

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[4] E. Steinegger and T. Reichstein, *Pharm. Acta Helv.* **22**, 258 (1947).

[5] O. R. Hansen, *Acta Chem. Scand.* **1**, 657, (1947).

[6] H. G. Boit, Chem. *Ber.* **87**, 1082, (1954).

[7] M.-M. Janot and J. Le Men, *Bull. Soc. Chim.* 1841, (1956).

[8] P. Potier, and J. Le Men, *Bull. Soc. Chim.* 456, (1959).

[9] S. Huneck, *Naturwiss* **49**, 233, (1962).

[10] P. Bladon, R. Ikan, F. S. Spring, and A. D. Tait, *Tetrahedron Letters* **No. 9**, 18, (1959).

In earlier publications we have described the identification of spermidine (I),[11] and 2,4'-dihydroxydiphenyl-3',5-dicarboxylic acid (II, R = H)[12] among the products of alkali fusion of this alkaloid. We now present further degradative evidence, which taken together with the spectroscopic properties, allows the formulation of lunarine as one of two possibilities (IIIa) and (IIIb).

Firstly, we have confirmed the structure of the dihydroxy diphenyldicarboxylic acid (II, R = H) by synthesis of the corresponding dimethyl ether (II, R = Me). This was effected by the mixed Ullmann reaction of methyl 3-iodo-4-methoxybenzoate and methyl 5-iodo-2-methoxybenzoate. The resulting mixture of esters was saponified and the acids were separated by counter-current distribution. The 2,4'-dimethoxydiphenyl-3'5-dicarboxylic acid (II, R = Me) was identical with material obtained by methylation of the degradation product (II, R = H) of lunarine.

A further diphenyl derivative produced by alkali fusion of lunarine is formulated as (IV).[13] This formulation is based on the reasonable assumption that the substitution in the diphenyl rings system is similar to that in the acid (II, R = H) described previously. The presence of the dihydrocoumarin ring was indicated by the carbonyl peak in the infrared spectrum of the

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[11] P. Potier, J. Le Men, M.-M. Janot, and P. Bladon, Tetrahedron Letters No.18, 36, (1960).

[12] P. Bladon, M. Chaigneau, M.-M. Janot, J. Le Men, P. Potier, and A. Melera, Tetrahedron Letters No.10, 321, (1961).

[13] The methoxyl groups were introduced in the isolation process which involved methylation with diazomethane at one stage.

methyl ester at 1786 cm.$^{-1}$ (dihydrocoumarin had $\nu_{max.}$ 1770 cm.$^{-1}$ cf.[14]). The nuclear magnetic resonance spectra of the acid (IV) (in dimethyl sulphoxide) and of its methyl ester (in carbon tetrachloride) showed aromatic proton resonance consistent with 1,2,4-substitution in both benzene rings. In addition, the spectrum of the methyl ester showed resonance due to two methoxy groups and also the expected two triplets due to the $A_2B_2$ system of the dihydrocoumarin ring.

Besides the diphenyl derivatives, alkali fusion of lunarine produced a mixture of monobenzenoid hydroxy acids (isolated as their methyl ethers[13]). This contained 3-methyl-(V,R = Me), 3-ethyl-(V, R = Et), and (most significantly) 3-propyl-4-methoxybenzoic acid (V, R = n-Pr). The first of these was identified by the isolation of its methyl ester, which was identical with a synthetic specimen, the other two were identified by comparative gas chromatography of their methyl esters alongside synthetic specimens.

The alternative structures (III) for lunarine can account satisfactorily for the formation of all these degradation products, by processes, well known to occur under conditions of alkali fusion,[15] such as those outlined in the chart.

These structures are also consistent with the nuclear

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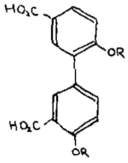
[14] J. Lecomte, *Handbuch der Physik* Vol.26, p.556. Ed. S. Flugge, Berlin, Springer, (1958).

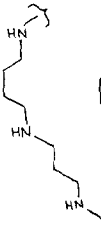
[15] R. G. Ackman, P. Linstead, B. J. Wakefield, and B. C. L. Weedon, *Tetrahedron* **8**, 221, (1960); R. A. Dytham and B.C.L. Weedon, *Tetrahedron* **8**, 246, (1960); **9**, 246, (1960).

$H_2N.(CH_2)_3.NH.(CH_2)_4.NH_2$

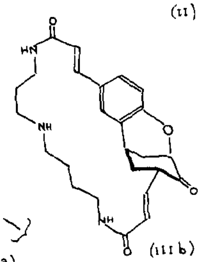
(I)



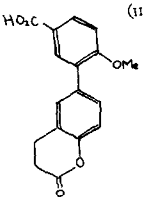
(II)



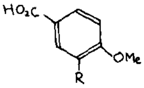
(IIIa)



(IIIb)



(IV)



(V)

magnetic resonance spectrum of lunarine,[16] which is shown in the figure, together with idealized assignments. The δ-keto-αβ-unsaturated amide hydrogen is responsible for the broad peak (o) at δ = 8.9; the shift to low field in this case is analogous to that recorded for the amide hydrogen in acetoacetanilide[17] the

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[16] The spectrum was obtained at 60 Mc/s using deuterochloroform as solvent. Chemical shifts are recorded as δ values, i.e. shifts to lower fields expressed at p.p.m. from the peak of tetramethylsilane as internal standard, see: N.S. Bhacca, L. F. Johnson, and J. N. Shoolery, N.M.R. Spectra Catalog, p.1. Varian Associates, Palo Alto (1962). Assignment of peaks was helped by the availability of a spectrum of the low field region in methanol as solvent.

[17] N.S. Bhacca, L. F. Johnson, and J. N. Shoolery, N.M.R. Spectra Catalog, spectrum No. 256, Varian Associates, Palo Alto, (1962).

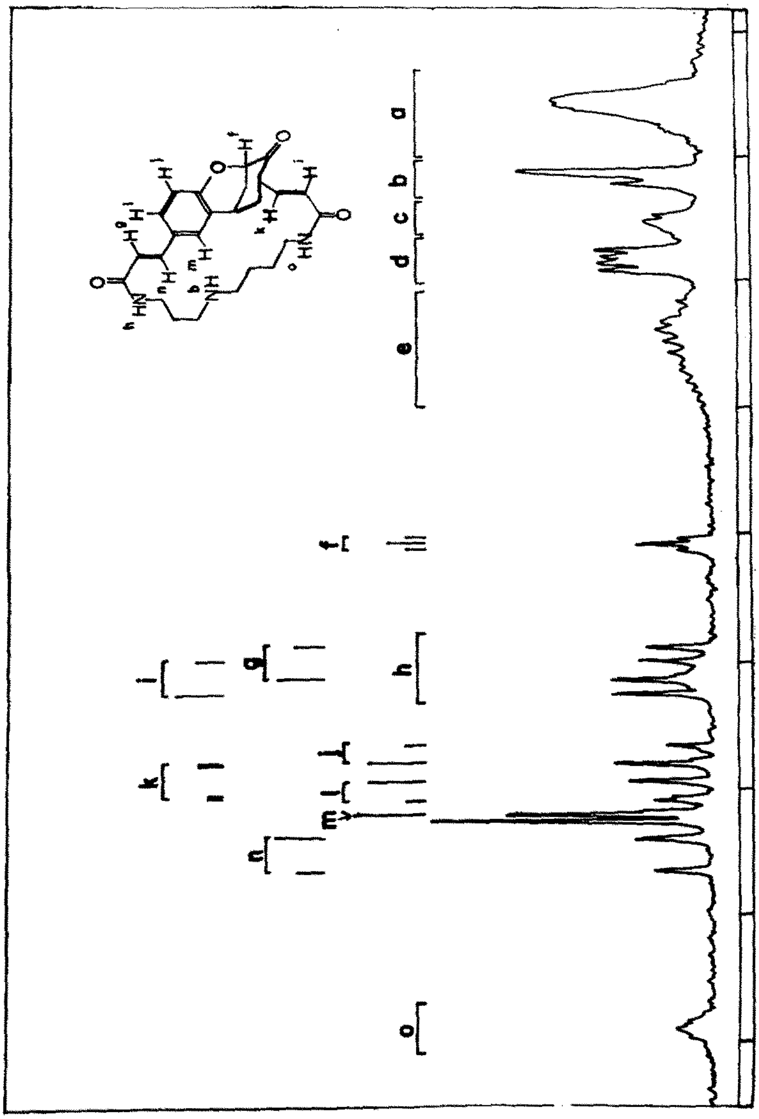
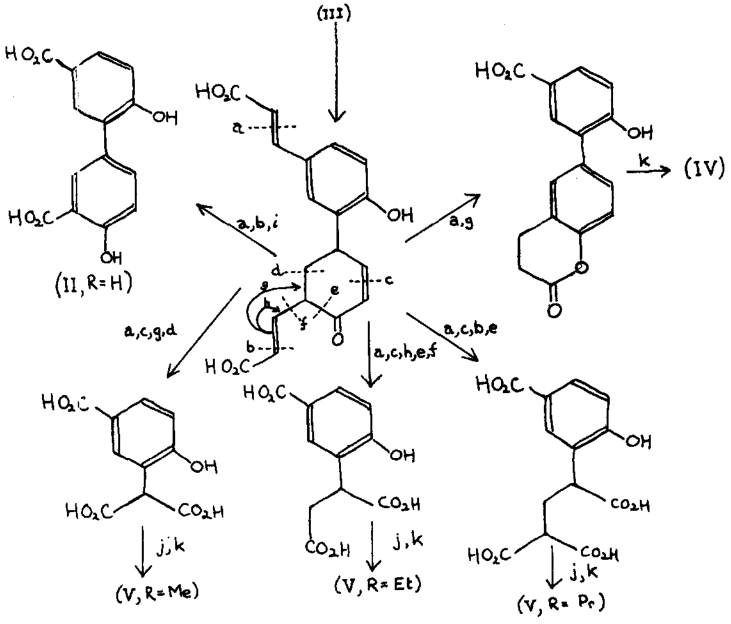


Fig. 1. Nuclear magnetic resonance spectrum of lunarine.

## Alkali Fusion of Lunarine



| | |
|---|---|
| **a,b,c,d,e,f.** | **bond fission** |
| **g,h** | **bond migration** |
| **i** | **oxidation (dehydrogenation)** |
| **j** | **decarboxylation** |
| **k** | **methylation with $CH_2N_2$ (in isolation process)** |

**The individual steps are understood to occur in the order indicated.**

**other amide hydrogen gives a broad peak (h) at δ = 6.10 submerged by four sharp peaks. These peaks comprise two pairs centred at δ = 6.00 (g) and δ = 6.10 (i) which are due to the α-protons of the cinnamamide and δ-keto-αβ-unsaturated amide systems respectively. The β-protons to which these are coupled (the identical coupling constants, J = 15.5 cps, are consistent with a <u>trans</u> double bond in both cases) give rise to the twin peaks centred at δ = 7.54 (n)**

and the quartet centred at $\delta = 6.90$ (k) respectively. In the latter case the small splitting due to coupling with the $\gamma$-hydrogen atom ($J \sim 2$ cps) is obscured by the overlying peaks of the aromatic hydrogens. These form the pattern expected for 1,2,4-benzenoid substitution: i.e. an AB quartet ($J = 7$ cps) the two halves of which at $\delta = 6.70$ (j) and $\delta = 7.00$ (l) are due to the <u>ortho</u> coupled hydrogens, and a single peak (m) at $\delta = 7.20$ due to the hydrogen without <u>ortho</u> neighbours. Weak <u>meta</u> coupling is seen as a broadening of peaks (l) and (m). The lone hydrogen on the carbon atom adjacent to the ketone group which also bears one end of the ether linkage gives rise to the triplet at $\delta = 5.10$ (f).

The formulae (IIIa and IIIb) also acount satisfactorily for the ultraviolet spectra of lunarine (Table I), when the basic assumption is made that the bathochromic shifts in alkali and in acid solutions are caused by two different chromophores.

<u>Table 1.</u> <u>Ultraviolet spectra of lunarine.</u>

| | $\lambda_{max.}$ mμ ($\varepsilon$) | |
|---|---|---|
| **Ethanol** | 0.1M NaOH | 10M HCl |
| 208 (29,200)<br>224 (26,000)<br>296 (22,100)<br>315 (17,300) | 224 (28,800)<br>355 (27,500) | 236 (24,200)<br>354 (24,400) |

As a model compound for the aromatic chromophore, 4-methoxy-3-methylcinnamamide was prepared. This had $\lambda_{max.}$ 213, 228, 308 mμ ($\varepsilon$, 15,900, 16,600, 22,500) in neutral solution, unchanged in alkali, but shifted to $\lambda_{max.}$ 240, 347 mμ ($\varepsilon$, 11,100, 25,700) in 10M hydrochloric acid. Direct analogies for the $\delta$-keto-$\alpha\beta$-unsaturated amide chromophore are not available.[18] However this

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[18] A remote analogy for the anion (i.e. spectrum in alkaline solution) is provided by the anion of cholest-5-ene-3,7-dione: $\lambda_{max.}$ 392 mμ. $\varepsilon$,62,200. See L.Dorfman, <u>Chem. Rev.</u> **53**, 47, (1953).

would be expected to absorb at 220-230 mμ in neutral solution and to show the large shift in alkaline solution to 350-360 mμ. To account for the disappearance of the cinnamamide chromophore in alkaline solution, we presume that the strain induced in the macrocyclic ring upon formation of the anion of the δ-keto-αβ-unsaturated amide, which would have the planar conformation is sufficient to cause the non-coplanarity of the cinnamamide side chain and the benzene ring.

A decision between the two structures (IIIa) and (IIIb) for lunarine is not possible on the available chemical evidence, but must await the results of X-ray crystallographic studies on lunarine hydrobromide now in hand.

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