Tetrahedron, 1958, Vol. 4, pp. 418–429. Pergamon Press Ltd., London

NOTES

The structure and substitution of the C–D ring system of delphinine

(*Received* 22 *July* 1958)

THE alkaloid delphinine ($C_{33}H_{45}NO_9$) is one of the most complex and most extensively investigated members of the Aconite–Delphinium–Garrya group. Mainly by the efforts of Jacobs[1] it has been shown to possess six rings, a tertiary nitrogen carrying an N-methyl group, an acetoxy, benzoxy and tertiary hydroxy group, and four methoxyls.

We have now derived the partial structure (I) for delphinine on the basis of experimental data of Jacobs[1] (which we have partly repeated and corroborated) as well as on the basis of our own experiments. The same partial formula also represents α-oxodelphinine which is an N-formyl compound. Pyro-α-oxodelphinine is represented by (II) and *iso*pyro-α-oxodelphinine which is obtained from (II) by methanolic HCl is portrayed by the formula (III). The transformation (II → III) is thus a shift of a double bond, with no skeletal rearrangement. The methoxyl in brackets represents the only alternative formulation of the pyro-*iso*pyro reaction, namely an allylic shift.

Hydrolysis of the benzoxy group in (III) gave the corresponding diol which Jacobs[2] oxidised to an αβ-unsaturated keto acid, now represented by (IV). Compound (IV) is easily isomerised[2] to the γ-lactone (V). Dihydro-α-oxo*iso*pyrodelphonine has been oxidised[3] to the corresponding ketone which we now represent by (VI).

Compound (VI) is transformed[3] by the action of alkali into the isomer formulated by us as (VII). Our own experimental evidence (vide infra) is concerned with the proof of this transformation. The reaction (VI → VII) is connected with a characteristic large laevorotatory change ($\Delta[\alpha]_D = -110$). Dihydro (II) may be saponified and oxidised[3] analogously to dihyro-α-oxo-delphonone (VIII) which is a diastereoisomer (and) or methoxyl-position-isomer of (VI). Treatment of (VIII) with alkali gives an isomeric ketone (IX). The reaction (VIII → IX) is accompanied by the same laevorotatory change as the reaction (VI → VII). This is strong evidence for the identical skeletal structure of (II) and (III).

The same series of reactions may also be performed with (I).[3] This gave both in Jacobs'[3] and our hands α-oxodelphonone (X), which may be isomerised by alkali to the *iso*delphonone (XI). The molecular rotational difference of the change (X → XI) is again the same as for the reaction (VI → VII). We have now confirmed the correctness of our formulations in the following manner.

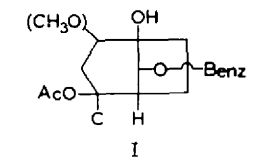
Compound (XI) takes up precisely one mole of periodic acid and gives acidic material which spontaneously on work-up eliminates a molecule of water and gives an acid (m.p. 187°), crystallising with half a mole of ethanol, and formulated as (XII). (Found: C, 61·70; H, 7·58; O, 28·02; N, 3·00; Calc. for $C_{24}H_{33}NO_8 \cdot \frac{1}{2}C_2H_5OH$: C, 61·70; H, 7·46; O, 27·99; N, 2·88%.) The ultra-violet spectrum of (XII) (λ_{max} 257 mμ, log ε = 4·1) indicates a trisubstituted αβ-unsaturated ketone. The infra-red frequency (1710 cm^{-1}) of the conjugated keto group is in agreement with a five-membered ring ketone.

Jacobs[3] has shown that oxidation of (X) with chromium trioxide gives a seco-acid which we now formulate as (XIII). We have also obtained (XIII) by treatment of α-oxodelphonine with periodic acid followed by neutralisation and treatment with permanganate. Compound (XIII) is completely stable to warm aqueous alkali. On the other hand, treatment of the oily methyl ester of (XIII) (I. R. 1706 cm^{-1} ketone, 1736 cm^{-1} ester) with methanolic sodium methoxide at reflux temperature followed by saponification gives the acid (XII) presumably via the diketone (XIV). All the reactions discussed constitute a rigorous proof of the partial formulae used in this communication.

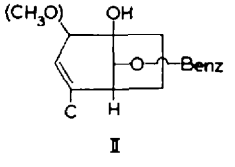
The sequence (XIII → XII) is made possible by the remarkable reluctance of the ester of (XIII) to

[1] For a summarising reference, see W. A. Jacobs and S. W. Pelletier, *J. Amer. Chem. Soc.* **78**, 3542 (1956).
[2] W. A. Jacobs and Y. Sato, *J. Biol. Chem.* **180**, 479 (1949).
[3] W. A. Jacobs and S. W. Pelletier, *J. Org. Chem.* **22**, 1428 (1957).

eliminate the β-hydroxyl. This is probably due to the strain of the resulting double bond. A simple explanation of this situation is the assumption that the *cyclo*heptane system in (XIII) is attached to the rest of the molecule by the two carbons "β" to the carboxyl.



I



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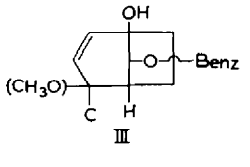
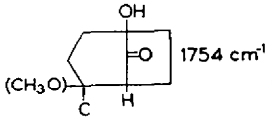
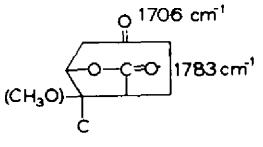


III



VI



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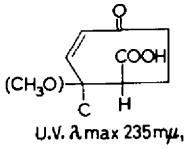
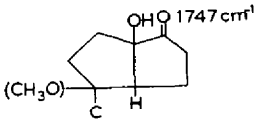
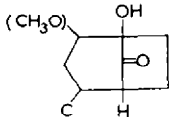


U.V. λ max 235 mμ, logϵ=3·8

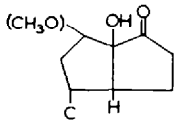
IV



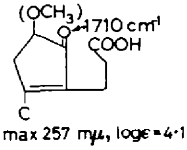
VII



VIII

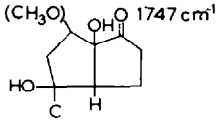


IX

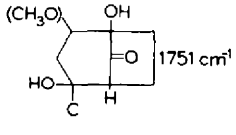


U.V. λ max 257 mμ, logϵ = 4·1

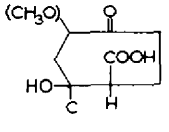
XII



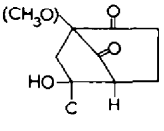
XI



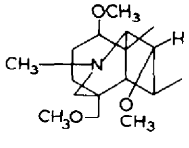
X



XIII



XIV



XV

In this case, of course, even the double bond in (II) is strained. However, consideration of models shows that the strain in (II) is definitely not intolerable. Moreover, (II) is formed by pyrolysis and is isomerised to (III) exceedingly readily.

It is striking that the partial structure of delphinine is a substituted bi*cyclo*(1,2,3)octane system which is the characteristic structural feature of all diterpenoid alkaloids or their biogenetic precursors.[4]

Thus we may assume that the partial structure (I) represents the C–D ring system of a diterpenoid alkaloid. For the rest of the molecule, the demethylation studies of Jacobs[5] are very pertinent. The fact that the A–B system is modified is indicated by a positive outcome of the first stage Hofmann degradation (cf. 3).

[4] Z. Valenta and K. Wiesner, *Chem. & Ind.* 354 (1956).
[5] W. A. Jacobs and S. W. Pelletier, *J. Amer. Chem. Soc.* **76**, 161 (1954).

We consider the partial structure (XV) as a biogenetically plausible, but unproved working hypothesis for the A, B and nitrogen rings of delphinine. This partial formula coincides to some extent with a structure proposal of Jacobs[1] which in turn is based on the typical diterpenoid alkaloid system.[6]

We intend to discuss the merits of (XV) and the complete structure of delphinine in conjunction with some experimental studies now in progress.

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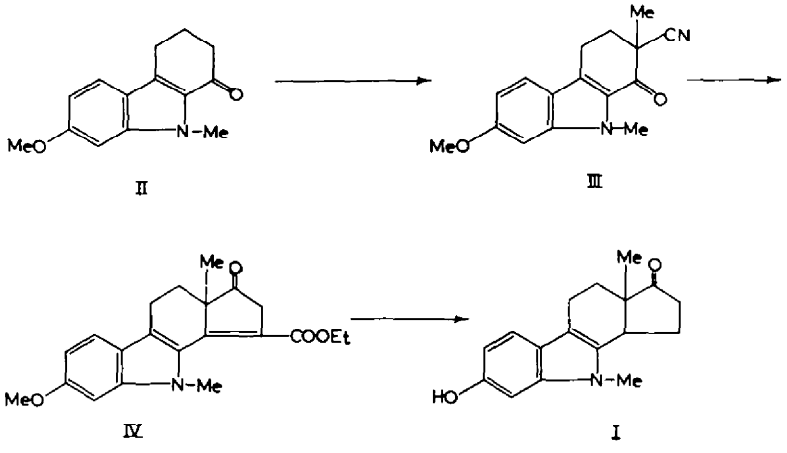
[6] K. Wiesner, D. R. Armstrong, M. F. Bartlett and J. A. Edwards, *Chem. & Ind.* 132 (1954); *J. Amer. Chem. Soc.* **76**, 6068 (1954).

Synthesis of 3-Desoxy-B-nor-6-aza-D-homoequilenin

(*Received* 26 *August* 1958)

THE synthesis of the pyrrolo analogue (I) of equilenin was attempted on the lines of the synthesis of thiopheno[1] and furano[2] steroids reported earlier by us. 7-Methoxy-9-methyl-1-oxo-1:2:3:4-tetrahydrocarbazole (II), m.p. 130°, prepared in three steps from 2-hydroxymethylene*cyclo*hexanone and *m*-methoxybenzenediazonium chloride, was converted into 2-cyano-2:9-dimethyl-7-methoxy-1-oxo-1:2:3:4-tetrahydrocarbazole (III), m.p. 156°, in the usual manner.[1,3] Compound (III), however, could not be converted into the tetracyclic pyrrolo-derivative (IV) by Stobbe condensation with diethyl succinate.



The synthesis of pyrrolo-steroids by an alternative route starting from *trans*-decalin-1:5-dione (V) was then undertaken. The latter (1 mol) and phenylhydrazine (1 mol) were boiled together in acetic

[1] R. B. Mitra and B. D. Tilak, *J. Sci. Industr. Res. India* **15 B**, 573 (1956) *Chem. Abstr.* **51**, 8790 (1957) and earlier papers.

[2] G. V. Bhide, N. L. Tikotkar and B. D. Tilak, *Chem. & Ind.* 1319 (1957).