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ALKALOIDS OF THE AUSTRALIAN RUTACEAE: HALFORDIA SCLEROXYLA. I. THE STRUCTURE OF N-METHYLHALFORDINIUM CHLORIDE.

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Alkaloids of the family Rutaceae show a wide range of structures[2], the only formal relationship between them being a general adherence to the anthranilic acid skeleton (I). Recent publication[3] of the oxazole structure for annuloline (II) (from L. multiflorum; Gramineae) prompts us to report the occurrence of a similar structure in the quaternary alkaloid (IIIa) isolated from Halfordia scleroxyla.

N-Methylhalfordinium picrate[4] ($C_{20}H_{23}O_4N_2^{\oplus}$ $C_6H_3O_7N_3^{\ominus}$), prepipitated from a purified bark extract, was obtained as an orange crystalline solid mp 143° or 198° (depending on the method of crystallisation). The yellow perchlorate (mp 148° or 206°) and chloride (mp 210° dec.) were prepared by anion exchange. Pyrolysis of the latter led to the expected loss

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[1] Taken from the Ph.D. thesis of J.H. Hodgkin.

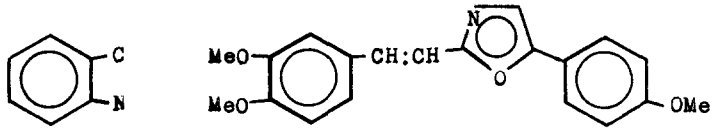
[2] L. Zechmeister "Progress in the Chemistry of Organic Natural Products", Vol. XIII, p. 303 et seq.

[3] R.S. Karimoto et al., Tetrahedron Letters, 1962, 83.

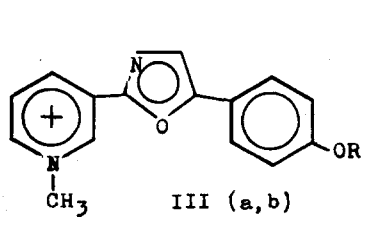
[4] Satisfactory analyses were obtained on all compounds.

of methyl chloride, generating the weak tertiary base halfordine (IVa: $C_{19}H_{20}O_4N_2$, mp 163°). The absence of skeletal rearrangement was shown by reversing this process in the usual manner.

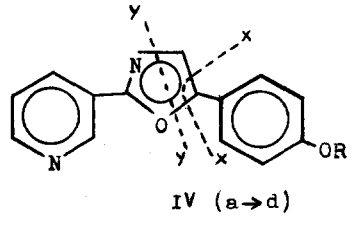
Halfordine showed no NH or CO bands in the infrared, but two OH bands ($\bar{\nu}$ 3602 and 3587 cm^{-1} in $CHCl_3$) were present. Their location was tentatively indicated by the presence of halfordinone (IVb: $C_{19}H_{18}O_3N_2$ - CO at 1728 cm^{-1}) as a minor pyrolysis product; its origin requires no comment.



I II



III (a,b)



IV (a→d)

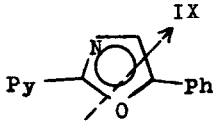
a: R= $-CH_2-CHOH-C(OH)Me_2$ c: R= -H

b: R= $-CH_2-CO-CHMe_2$ d: R= -Me

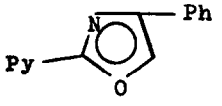
Conclusive evidence for the hydroxylated isoprenyl ether function was obtained by strong acid hydrolysis, which led to halfordinol (IVc: $C_{14}H_{10}O_2N_2$, mp 255°) plus a variety of volatile fragments. These were identified (VPC and IR) as acetone, propan-2-ol (a major product under reducing conditions) and 1-hydroxy-3-methylbutan-2-one. Periodate fission led to

the production of acetone (cf. evoxine[5]). The mass spectra of halfordine and its O-acetate were consistent with the side chain structure allotted.

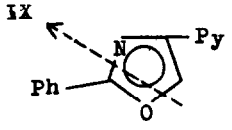
Permanganate oxidation of O-methylhalfordinol (IVd) gave anisic acid (fission x - x); halfordine itself (IVa) gave p-carboxyphenoxyacetic acid, thus incidentally confirming the site of attachment of the alkyl chain. The location of both N-atoms was shown by the isolation of nicotinamide (fission y - y) as a second product of oxidation, leaving only one carbon atom to be accounted for. Vigorous catalytic reduction of halfordinol methochloride (IIIc; from acid hydrolysis of IIIa) afforded an amide $C_{15}H_{28}ON_2$, (V) which contained all but one atom of the alkaloid skeleton, and proved to be the key degradation product of the series. The oxygen atom present



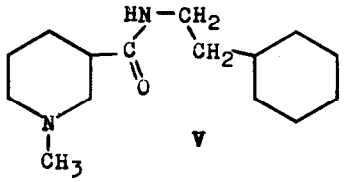
VI



VII



VIII



V

IX

must have arisen from hydrogenolysis of a ring, since the

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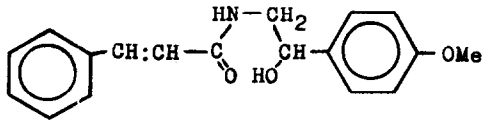
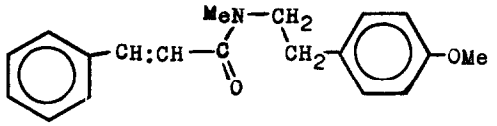
[5] F.W. Eastwood, G.K. Hughes and E. Ritchie, Aust. J. Chem. 7, 273 (1954).

4'-phenolic oxygen could not conceivably give rise to an amide (it is evidently lost by dehydration/reduction under the acidic conditions of reduction). The three oxazole structures VI-VIII (rings formalised as pyridyl and phenyl) remain as possible structures. The mass cracking pattern of halfordinol showed a peak at M/e = 121 (122 on deuteration) assigned to the ion IX (thus eliminating VII) while the absence of C-methyl in the amide eliminated VIII. Deuteration studies confirmed that the amide was secondary, which established the original site of quaternisation as the pyridine nitrogen. The identity of the amide V (corresponding to structure VI) was confirmed synthetically by hydrogenation of N-nicotinoyl-2-phenylethylamine, followed by Eschweiler/Clark methylation. The 60 Mc NMR spectrum of O-methylhalfordinol, and the mass spectrum of halfordinol were in accord with the structures IVd and IVc respectively. These, together with synthetic work now in progress, will be reported in a later communication.

The N-methylhalfordinium ion represents an interesting problem from the biogenetic point of view. Although it does not possess the fragment I (it is not alone in this among alkaloids of the Rutaceae), the conversion of anthranilic to



X



XI

nicotinic acid is a well known metabolic pathway[6]; the presence of the nicotinamide moiety is thus not surprising. The oxazole nucleus could well arise from a type of precursor common to that which produces the amides aegelin[7] (X) and O-methyl-tyramine-N-methylcinnamide[8] XI, which have an obvious resemblance in general pattern to annuloline.

Acknowledgments

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8 F.B. La Farge and W.F. Barthel, J. Org. Chem. 9, 250 (1944).