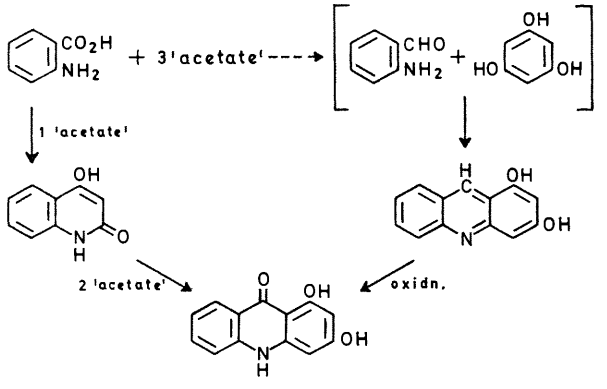
The Biogenesis of Acridone† Alkaloids

By I. H. BOWEN, P. GUPTA and J. R. LEWIS*
(*Department of Chemistry, University of Aberdeen, Old Aberdeen* AB9 2UE)

Summary The similarity in substitution pattern between xanthones and acridone alkaloids and the analogous cyclisation reactions observed for 2-hydroxy- and 2-amino-benzophenones suggest that related biogenetic pathways may be involved.

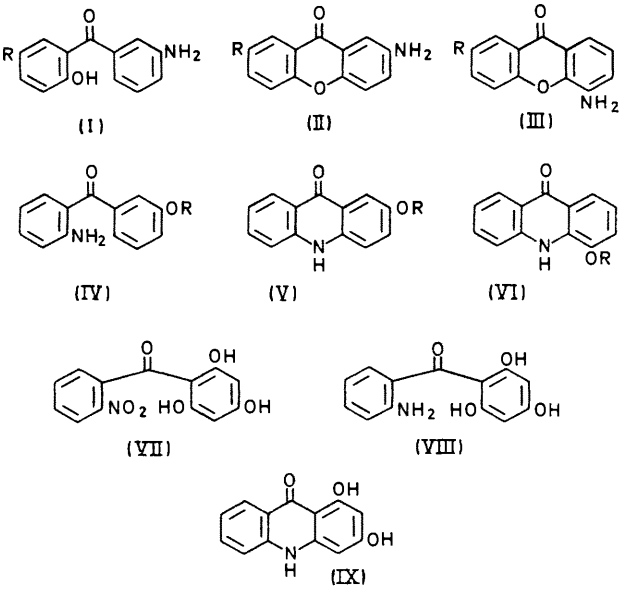
IT has been suggested that in the biogenesis of the acridone alkaloids, anthranilic acid and 'acetate' are involved[2] and some support for this has been obtained by ^{3}H-labelled anthranilic acid incorporation into *Glycosmis*,[3] *Evodia*, and *Melicope*[4] generated alkaloids. However, the synthesis of the acridan-9-one ring system under 'physiological-type' conditions remains centred around the observation by Hughes and Ritchie[5] that 2-aminobenzaldehyde and phloroglucinol condense readily to give the acridine which can then be oxidatively converted into 1,3-dihydroxyacridan-9-one. Prager and Thredgold[4] also suggest, from feeding experiment data, that a quinolone and two acetate units may be involved (see Scheme 1) in the biogenesis.

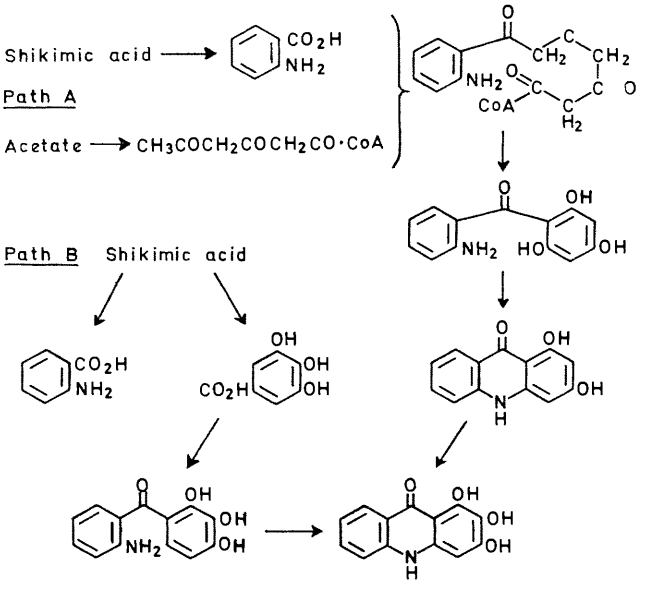


SCHEME 1

We have considered that the similarity in hydroxylation pattern of xanthones and acridones suggests that a biogenetic relationship may exist between them and that acridones could be derived from 2-aminobenzophenones by oxidative coupling and/or by intramolecular dehydration, as has been found for xanthones.[6,7] The role played by both the *shikimate* and *acetate* pathways in xanthone biogenesis[8] also supports this suggestion.

The capability of the amino-group to participate in the oxidative cyclisation of benzophenones was established by





SCHEME 2

† "Acridone" is to be preferred to "acridine," the original description for these alkaloids.[1]

the conversion of 2-hydroxy-3′-aminobenzophenone (**I**; R = H or Me) into a mixture of 2-amino- and 4-amino-xanthone (II and III; R = H or Me)[9] using potassium ferricyanide or potassium dichromate in acid or alkaline solution (up to 87% conversion). In the case of 2-amino-3′-hydroxybenzophenone (IV; R = H) oxidative cyclisation to 2-hydroxy- and 4-hydroxy-acridan-9-one (V and VI; R = H) only occurred with manganese triacetate or potassium persulphate in 14 and 8% yield, respectively. The methoxy compound (IV; R = Me) behaved in a similar manner.

The cyclodehydrative process was observed when quantitative conversion of 2-nitro-2′,4′,6′-trihydroxybenzophenone (VII) into 1,3-dihydroxyacridan-9-one (IX) [presumably *via* the 2-aminobenzophenone (VIII)], took place in the presence of Sn/HCl at room temperature.

The biogenesis of the acridone alkaloids utilising 2-aminobenzophenone intermediates can be summarised in Scheme 2; however the co-occurrance of 1,3-dioxygenated and 1,2,3,4-tetraoxygenated acridone alkaloids in *Acronychia*[10] suggests path A with or without hydroxylation as being the most probable route.

A number of benzophenones and related compounds have been screened for anti-tumour activity[11] and show inhibition to the growth of *Physarum polycephalum*.

All new compounds have satisfactory spectral data and analyses.

We thank the S.R.C. for a Studentship (I.H.B.), the Cancer Research Campaign for a Fellowship (P.G.) and G.E.C.A. for screening results.

(*Received, August 13th*, 1970; *Com.* 1367.)

[1] J. R. Price, *Fortschr. Chem. org. Naturstoffe*, 1956, **13**, 302.
[2] E. Leete, *Rev. Plant Physiol.*, 1967, **18**, 179.
[3] D. Gröger and S. Johne, *Z. Natursforsch.*, 1968, **23**b, 1072.
[4] R. H. Prager and H. M. Thredgold, *Austral. J. Chem.*, 1969, **22**, 2627.
[5] G. K. Hughes and E. Ritchie, *Austral. J. Sci. Res.*, 1951, A**4**, 423.
[6] J. R. Lewis and B. H. Warrington, *J. Chem. Soc.*, 1964, 5074.
[7] J. E. Atkinson and J. R. Lewis, *J. Chem. Soc.* (*C*), 1969, 281.
[8] J. E. Atkinson, P. Gupta, and J. R. Lewis, *Chem. Comm.*, 1968, 1386.
[9] I. H. Bowen, Thesis, 1967, University of Aberdeen.
[10] G. H. Svoboda and R. W. Kattan, *Lloydia*, 1967, **30**, 364.
[11] N.R.D.C., U.K. Patent Application No. 23874/70.