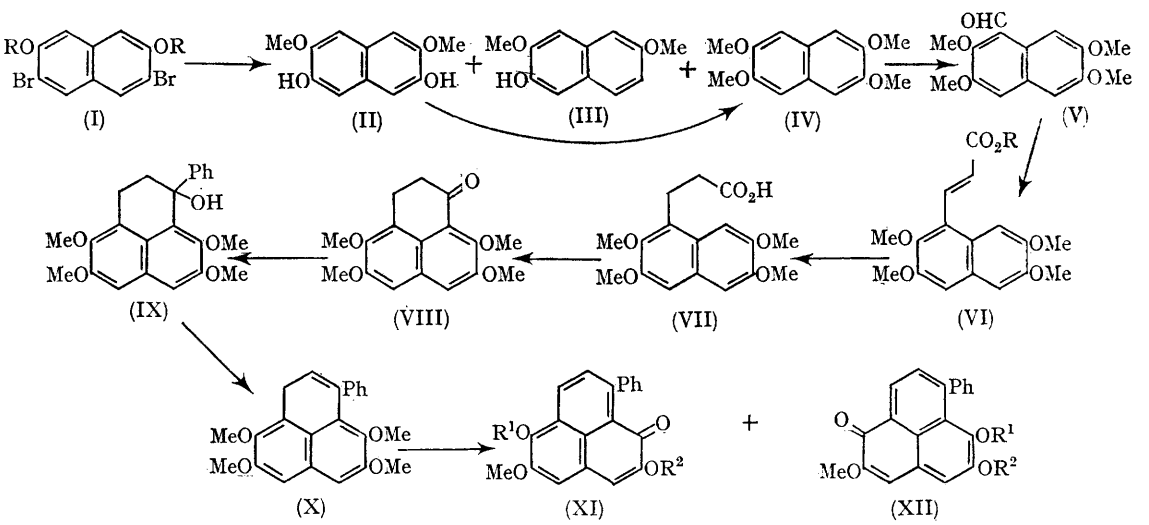
Synthesis of Haemocorin Aglycone

By B. LAUNDON and G. A. MORRISON*

(*Department of Organic Chemistry, The University, Leeds* 2)

THE plant glycoside haemocorin is one of a small group of natural products which have structures based on the phenalenone nucleus. Other members of this group are atrovenetin,[1] herqueinone,[1] and resistomycin;[2] dimeric variants are also known, *e.g.* duclauxin.[3] Degradative studies have revealed that haemocorin aglycone is to be represented by the structure (XI; $R^1 = R^2 = H$) or the tautomeric form (XII; $R^1 = R^2 = H$).[4] Because of the possibility of tautomerism, haemocorin aglycone affords two monomethyl ethers, *A* (XI; $R^1 = Me$, $R^2 = H$) and *B* (XII; $R^1 = Me$, $R^2 = H$) and two dimethyl ethers, *A* (XI; $R^1 = R^2 = Me$) and *B* (XII; $R^1 = R^2 = Me$). Here we describe the synthesis of the two dimethyl ethers. We have also obtained the third possible monomethyl ether of the aglycone, hitherto unknown, which has the structure (XI; $R^1 = H$, $R^2 = Me$) or the tautomeric form (XII; $R^1 = H$, $R^2 = Me$). Since the dimethyl ether *A* has previously been hydrolysed to the aglycone[4b] the sequence described below permits the synthesis of haemocorin aglycone itself, which thus becomes the first naturally occurring phenalenone to be obtained by synthesis.

3,6-Dibromonaphthalene-2,7-diol (I; R = H)[5] was converted into its dimethyl ether (I; R = Me) and the latter was lithiated, with n-butyl-lithium. Treatment of the lithio-derivative with methyl borate followed by oxidation with hydrogen peroxide[6] gave a mixture of 2,7-dimethoxynaphthalene-3,6-diol (II) and 2,7-dimethoxy-3-naphthol (III) which were obtained pure in yields of 43% and 21% respectively. Methylation of the dihydric phenol (II) afforded the symmetrical tetramethoxynaphthalene (IV), which was converted into the aldehyde (V) in 60% yield by means of a Vilsmeier reaction. The aldehyde (V) was converted in quantitative yield into the unsaturated acid (VI; R = H) by first treating it, in a Wittig reaction, with ethoxycarbonylmethylenetriphenylphosphorane, and then saponifying the ester (VI; R = Et) thus obtained. Hydrogenation of the acid (VI) gave the tetramethoxynaphthalenepropionic acid (VII) (87% yield).



Cyclisation of (VII) to give the tetramethoxyphenalanone (VIII) in 58% yield was achieved with polyphosphoric acid. Addition of phenylmagnesium bromide to compound (VIII) proceeded quantitatively to give the carbinol (IX), which was dehydrated to give 4,5,8,9-tetramethoxy-3-phenylphenalene (X) in a yield of 77% after purification. The structure of the phenalene (X) followed from

its n.m.r. spectrum: 3-proton singlet at τ 6·91 (4-OMe group); 6-proton singlet at 6·14 and 3-proton singlet at 6·07 (5,8,9-OMe groups); 2-proton doublet at 6·11, J 4·5 c./sec. (CH_2); 1-proton triplet at 4·07, J 4·5 c./sec. (2-H atom); 1-proton singlets at 3·14 and 3·09 (aromatic H atoms); 5-proton singlet at 2·72 (Ph).

When the phenalene (X) was hydrolysed by being heated with aqueous methanolic hydrochloric acid and the crude product was dehydrogenated with 2,3-dichloro-5,6-dicyanobenzoquinone a mixture of haemocorin aglycone dimethyl ethers *A* (XI; $R^1 = R^2 = Me$) (8% yield) and *B* (XII; $R^1 = R^2 = Me$) (20% yield) was obtained which was separated by preparative layer chromatography on Kieselgel.

Acid hydrolysis of either of the dimethyl ethers gave initially a violet-coloured phenol which, from its n.m.r. spectrum, contained two methoxy-groups. Upon methylation it gave a mixture of dimethyl ethers *A* and *B*, and we have accordingly designated it as the aglycone monomethyl ether *C* (XI; $R^1 = H$, $R^2 = Me$) or the tautomeric form (XII; $R^1 = H$, $R^2 = Me$). Monomethyl ether *C* afforded two monoacetates which are tentatively assigned structures (XI; $R^1 = Ac$, $R^2 = Me$) and (XII; $R^1 = Ac$, $R^2 = Me$) on the basis of the acetoxy-group methyl signals which appear in their n.m.r. spectra at τ 7·53 and 8·53 respectively.

Satisfactory analyses and spectra were obtained for all the new compounds described.

We are indebted to Dr. R. Thomas of Imperial College, London, for kindly providing us with authentic samples of haemocorin aglycone and its methyl ethers for purposes of comparison.

(*Received, September 26th*, 1968; *Com.* 1314.)

[1] D. H. R. Barton, P. De Mayo, G. A. Morrison, W. H. Schaeppi, and H. Raistrick, *Tetrahedron*, 1959, **6**, 48; G. A. Morrison, I. C. Paul, and G. A. Sim, *Proc. Chem. Soc.*, 1962, 352; I. C. Paul and G. A. Sim, *J. Chem. Soc.*, 1965, 1097.
[2] N. A. Bailey, C. P. Falshaw, W. D. Ollis, M. Watanabe, M. M. Dhar, A. W. Khan, and V. C. Vora, *Chem. Comm.*, 1968, 374.
[3] S. Shibata, *Chem. in Britain*, 1967, **3**, 110.
[4] (*a*) R. G. Cooke and W. Segal, *Austral. J. Chem.*, 1955, **8**, 107; (*b*) *idem., ibid.*, p. 413; (*c*) R. G. Cooke, B. L. Johnson, and W. Segal, *ibid.*, 1958, **11**, 230.
[5] R. G. Cooke, B. L. Johnson, and W. R. Owen, *Austral. J. Chem.*, 1960, **13**, 256.
[6] *Cf.* M. F. Hawthorne, *J. Org. Chem.*, 1957, **22**, 1001.