Synthesis of Bikaverin

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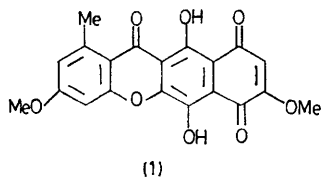
Summary Bikaverin (**1**) is synthesised from orcinol and nitrile (**3**) *via* (**4**)—(**7**).

BIKAVERIN (**1**) is a wine red pigment with specific anti-protozoal activity whose structure was recently determined.[1-3]

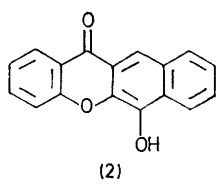
Our synthesis of the 6-hydroxy-12*H*-benzo[*b*]xanthen-12-one (**2**) system,[4] not previously encountered in natural products, prompted the synthesis of bikaverin reported here. 2,4,5-Trimethoxybenzaldehyde[5] was condensed with acetonitrile at 80° (benzene solvent) in the presence of Triton B, followed by catalytic hydrogenation, to give 2,4,5-trimethoxyhydrocinnamonitrile (**3**) (72%), m.p. 64°. The nitrile (**3**) was condensed with anhydrous orcinol at room temperature in dry nitrobenzene in the presence of $ZnCl_2$–HCl to give (**4**; X = H) (70%).

Treatment of (**4**; X = H) with diethyl oxalate in the dry tetrahydrofuran containing anhydrous NaOEt (6 equiv.) at room temperature gave (4; X = CO·CO_2Et) (40%). The crude product was azeotroped (benzene–toluene-*p*-sulphonic acid) to give the ethoxycarbonylchromone (**5**; R = H) (90%), m.p. 185°. Methylation ($MeSO_4$–K_2CO_3–acetone) at reflux gave (**5**; R = Me) (90%), m.p. 130°. Hydrolysis (1N-KOH in EtOH, overnight at room temperature) of (**5**; R = Me) to the corresponding acid and cyclisation of the derived acid chloride with BF_3,OEt_2 in CH_2Cl_2 gave the phenol (**6**), m.p. 243° (77%). Oxidation of (**6**) with potassium dichromate in glacial acetic acid at room temperature gave the known quinone[2] (**7**)† (58%). Demethylation of (**7**) ($AlCl_3$ in nitrobenzene, or preferably LiI in methyl t-butyl ketone at reflux[6]) gave bikaverin† (**1**) (80%). This route provides a useful way of preparing substantial quantities of bikaverin (**1**) and analogues.

All new compounds gave satisfactory spectral and microanalytical data.



(1)



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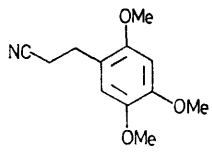

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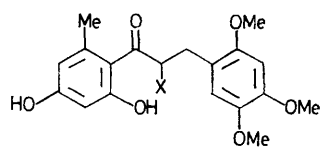

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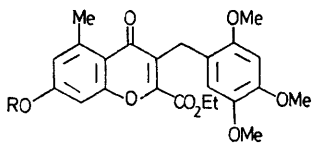

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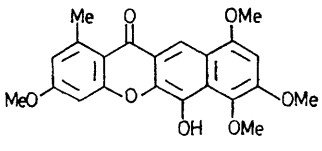

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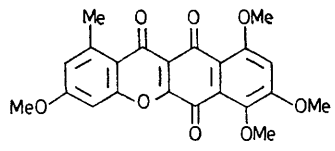

(7)

Independent synthetic approaches to bikaverin are being made elsewhere.[7]

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† Comparison with authentic samples, carried out by Professor Kjaer, showed them to be identical.

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[6] *Cf.* F. Elsinger, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, 1960, **43**, 113.
[7] Prof. A. Kjaer, personal communication.