Novel Synthesis of Pretetramid

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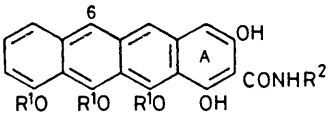
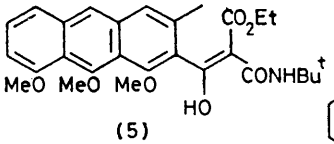
Summary A total synthesis of pretetramid is described.

PRETETRAMID (**2**) and its 6-methyl analogue are accepted precursors of the tetracycline antibiotics.[1] Both have been synthesised.[2,3] We now report a new synthesis of (**2**) which extends earlier work in which the anthracene (**1**) was synthesised by two routes.[4,5]

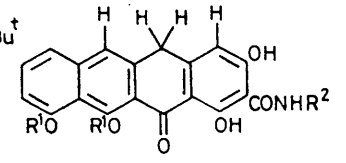
(1) R = H, X = OEt
(3) R = Me, X = OH
(4) R = Me, X = Cl



(2) $R^1 = R^2 = H$
(6) $R^1 = Me$, $R^2 = Bu^t$



(5)



(7) $R^1 = Me$, $R^2 = Bu^t$
(8) $R^1 = R^2 = H$

The phenol (**1**) was methylated (CH_2N_2) and the methyl ether† then converted by standard reactions (KOH then PCl_5) *via* the acid (**3**) into the acid chloride (**4**). This reacted *in situ* with a suitable malonate reagent following the model reaction described in the preceding communication[6] to give the derivative (**5**). The ^1H n.m.r. spectrum of this product showed that in $CDCl_3$ it exists as a single tautomer in which the ethyl group is forced to be over the plane of the aryl ring where it experiences a strong shielding effect (δ 0·44 and 3·69). Treatment with lithium di-isopropylamide (10 equiv.) in tetrahydrofuran at −78 °C followed by warming to room temperature gave (**6**) as a red solid in good yield (63%). From the spectroscopic data this compound appears to exist as a mixture of keto–enol tautomers in ring A. It is unstable and undergoes demethylation under mild conditions with dilute H_2SO_4 to give the stable derivative (**7**). This exists in CD_2Cl_2 as a single tautomer in which a potentially phenolic ring is non-aromatic. The structure was assigned on the basis of the n.m.r. spectrum which showed the key methylene peak at δ 4·36; irradiation at this frequency caused the two singlets arising from the flanking protons to sharpen without affecting the rest of the spectrum.

Complete removal of the protecting groups from (**6**) was achieved by treatment with hydrobromic acid in phenol at 100 °C. The product, pretetramid (**2**), was obtained as a microcrystalline solid which decomposed on heating at 323—327 °C (lit.[2] 290—320 °C). The u.v. spectroscopic data agreed well with the values reported by McCormick.[2] The compound is too insoluble in normal solvents for an n.m.r. spectrum to be recorded satisfactorily but a sufficiently strong solution was prepared in $(CD_3)_2SO$ containing magnesium trideuterioacetate (1%). Under these conditions the major tautomer was not the naphthacene (**2**) but the keto form (**8**); the methylene signal appeared at δ 4·03 and irradiation at that frequency caused the two singlets at δ 5·92 (1H) and δ 6·63 (1H) to sharpen. The

† All new compounds except (**4**) were fully characterised by spectroscopic and analytical data.

remaining signals occurred at δ 6·42 (1H, d, *J* 7·5 Hz), 6·87 (1H, d, *J* 7·5 Hz), 7·26 (1H, t, *J* 7·5 Hz), 7·68 (br, 1H), and 10·50 (br, 1H). Finally the mass spectrum showed only two major peaks at *m/e* 351 (M^+) and 334 ($M^+ - NH_3$).

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