A Novel Base-induced Cyclisation to produce an Aryl Ring

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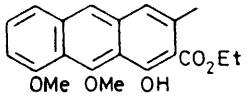
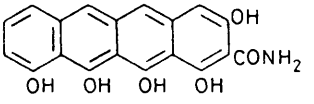
Summary Naphthalenes are produced from benzene derivatives by novel base-induced cyclisations of attached polycarbonyl residues.

THE recently reported[1,2] syntheses of the polyketide anthracene (**1**) open a new avenue to more elaborate polyketide natural products such as pretetramid (**2**), a biosynthetic precursor of certain tetracycline antibiotics.[3] As a model for the conversion of (**1**) into (**2**) we have examined methods for converting the benzene derivative (**3**) into the naphthalenes (**12**)—(**14**).



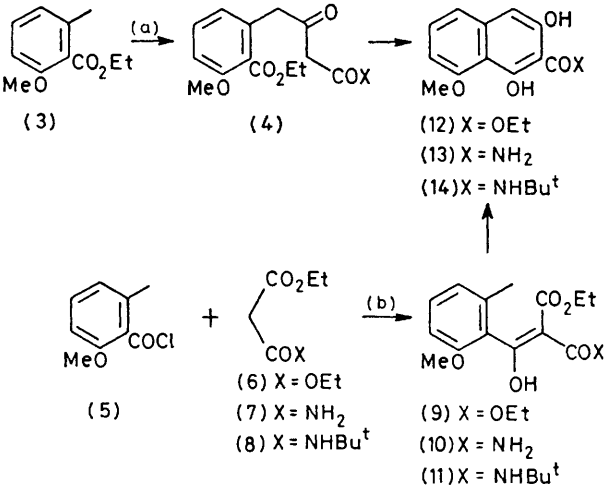
(1)



(2)

Initial efforts were directed towards route (a) by which it was hoped to acylate the methyl group of (**3**) using a suitable malonate reagent to give an intermediate (**4**). However, reaction of the anion derived from (**3**)[2] with diethyl malonate or Meldrum's acid[4] under a variety of conditions failed to give the desired products.

An alternative strategy (b) was therefore adopted in which the overall order of carbon–carbon bond formation is reversed. The acid chloride (**5**),† derived from (**3**) by standard methods, was used to acylate the anions of suitable malonate reagents. In this way (**9**) was prepared in excellent yield by reaction of (**5**) with the sodium salt of (**6**) in tetrahydrofuran (THF). In chloroform solution the product exists as an equilibrium mixture of the enol form with a smaller amount of the ketone tautomer (3 : 1). The ^{1}H n.m.r. signals for one of the two ethyl groups in the enol form are considerably upfield of those of the other (δ 0·82 and 3·87 *vs.* 1·37 and 4·34) showing that the enol system is twisted out of the plane of the benzene ring so that one ester group is held over the aryl system where it experiences a shielding effect. The cyclisation to produce (**12**), m.p. 113—114 °C, was achieved in good yield (68%) by adding lithium di-isopropylamide (4 equiv.) to a solution of (**9**) in THF at −78 °C followed by slow warming to room temperature.



The two amides (**10**) and (**11**) were prepared similarly by reaction of (**5**) with the sodium salts of (**7**) and (**8**) in THF. In each case the ^{1}H n.m.r. spectrum is consistent with a single enol tautomer in which the ethyl group is constrained to be in the shielding zone of the aryl ring. The stereochemistry is therefore as shown which is ideal for the

† All new compounds gave spectroscopic and analytical data consistent with the assigned structures.

desired cyclisations. These were carried out as described above but with 5 mol of base. The yield of (**13**), m.p. 203—206 °C, was poor (25%) but the conversion of (**11**) into (**14**) (m.p. 145 °C), was high (87%) and therefore this approach was selected for the subsequent synthesis of pretetramid.

The mechanism of the cyclisation deserves comment since in the reactive intermediate produced by deprotonation the formally nucleophilic and electrophilic centres are joined by a π-system through which they may be conjugated. The intermediate may therefore be viewed as a polyene which undergoes a pericyclic ring closure at a remarkably low temperature; related cyclisations in which ring closure is initiated by photoenolisation have been studied recently.[5]

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