STUDIES TOWARDS THE SYNTHESIS OF FREDERICAMYCIN A.

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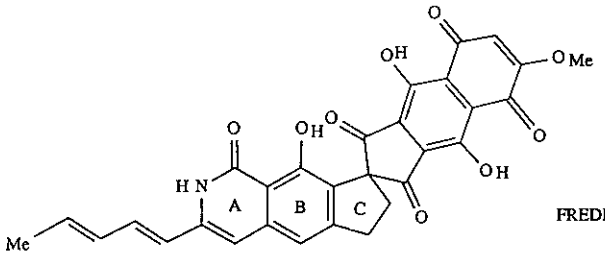
Dedicated to Sir Derek Barton on the occasion of his seventieth birthday.

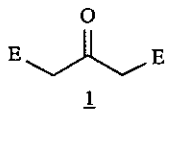
Abstract - An isocoumarin tricyclic ester related to rings ABC of the title compound has been synthesized. The possibility of exchanging the heterocyclic oxygen atom for nitrogen and of using an ester group for the construction of the side chain has been checked on a model compound.



FREDERICAMYCIN A

Fredericamycin A [1], produced by a strain of Streptomyces griseus, is an antitumour antibiotic. The molecule presents an unusual [2a] heterocyclic system cyclopent[g]isoquinoline (rings ABC).

E=COOEt



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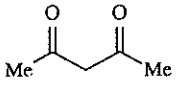

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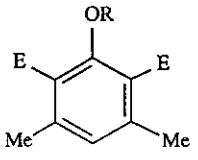
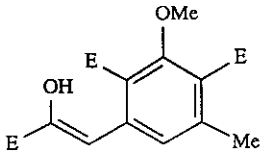


3 R=H
R=Me



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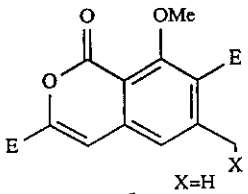
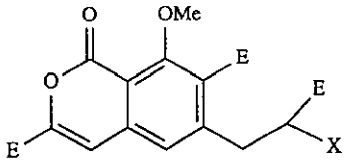
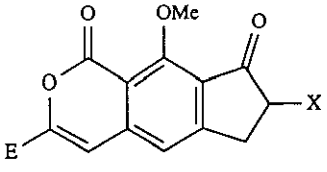


5 X=H
X=Br



6 X=COOEt
X=COO^{t}Bu
X=H

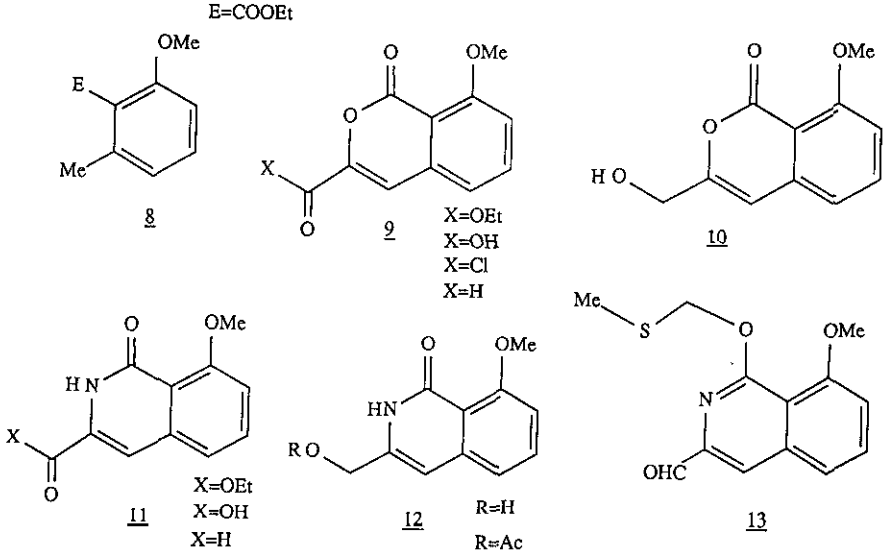


7 X=COOEt
X=H

This has been synthesized starting from an indene [2b] (rings B+C), from a pyridone [2c] (ring A) derivative or a polyketo ester [2d]. An isoquinoline derivative with an appending hemiacetal ring has been synthesized [2e]. We describe in this communication another route starting with the middle ring B. A key point is the construction of the analogous isocoumarinic derivative. The exchange of a nitrogen for the oxygen atom and the use of a carbethoxy group as the latent unsaturated side chain have been checked on a model compound. The use of an isocoumarin ring during most of the synthesis removes the difficulties associated with the protection- deprotection of the isoquinoline nitrogen atom.

The symmetrical diester 3, R = Me, readily available (88 %) starting from diethyl acetone-dicarboxylate and acetylacetone [3], was metalated with LDA on one of the methyl groups [4] and condensed with diethyl oxalate to give, after cyclisation with hot formic acid, [5] the isocoumarin ester 5, X = H, mp 101°C (94 %) [13]. Bromination with NBS gave the bromomethyl derivative 5, X = Br, mp 132°C (74 %) which was treated with t-butyl ethyl malonate to give 6, X = COOt-Bu. The t-butoxycarbonyl group was removed by heating with p-toluenesulfonic acid (84 % from 5, X = Br) The triester 6, X = H, mp 83°C, was then cyclised with sodium ethoxide in ethanol in the Dieckmann way to give the keto ester 7, X = COOEt, mp 188°C (79 %). Decarbethoxylation was carried out with the Krapcho technique [6] and gave the tricyclic keto ester 7, X = H, mp 214°C (92 %).

Hydrindanones like 7, X = H can be converted into the homologous aldehydes through the enol ether [7], the carbonitriles [8] or the carboxylic acids [9,10]. Hydrindane -1- carboxylic acid has been used to synthesize a model spiro system [10].



8-Methoxyisocoumarin-3-carboxylic acid ethyl ester 9, X = OEt, mp 140°C, was prepared (55 %) from 2-methoxy-6-methylbenzoic acid ethyl ester 8 and diethyl oxalate [4,5]. Hydrolysis with HCl gave the acid 9, X = OH, mp 258°C (90 %) which was converted with thionyl chloride into the acid chloride. Reduction of 9, X = Cl, with $LiAlH(O^t\text{-}Bu)_3$ gave isocoumarin-3-methanol 10 mp 131°C (76 % from 9, X = OH), which was treated with ammonium acetate[11] to give 3-acetoxy-8-methoxyisoquinolinone 12, R = Ac (89 %). Alternatively the isocoumarin ester 9, X = OEt, was converted under the same conditions into the corresponding isoquinolinone ester 11, X = OEt, mp 107°C (96 %). Reduction of 11, X = OEt, with sodium borohydride in t-butanol-methanol [12] then gave the isoquinolinone-3- methanol 12, R = H, mp 213°C (93 %). Reoxidation was carried out using the Swern technique ; an aldehyde was first formed which contained the methylthiomethyl enol ether of the amide function 13, mp 193°C (74 %). The hemithioacetal group was readily hydrolysed with hydrochloric acid to give the desired isoquinolone aldehyde 11, X = H, mp 225°C (98 %). Such an aldehyde has been used to synthesize the pentadienyl side chain of *fredericamycin* [2b].

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13 All new compounds gave analytical and spectral data in agreement with their structures.

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