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A CONVERGENT SYNTHESIS OF INDOLOQUINONES

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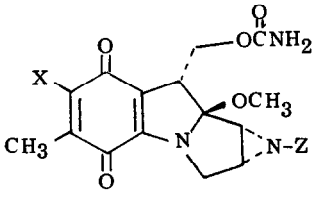
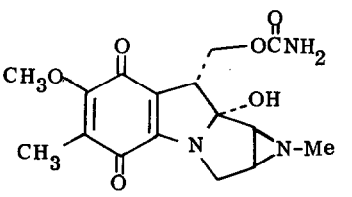
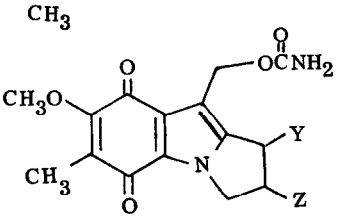
The novel structures of the mitomycins (1),[1] antibiotics with antibacterial and antitumor activity,[2] have been the targets of many synthetic approaches,[3] one of which has led to the total synthesis of Mitomycins A and C.[4] The complex functionality of these compounds and of the mitosenes (2),[5] indoloquinone derivatives of the mitomycins, suggests that convergence in their synthesis would be particularly advantageous.



	X	Z
1a Mitomycin A	CH_3O	H
1c Mitomycin C	H_2N	H
1d Porfiromycin	H_2N	CH_3

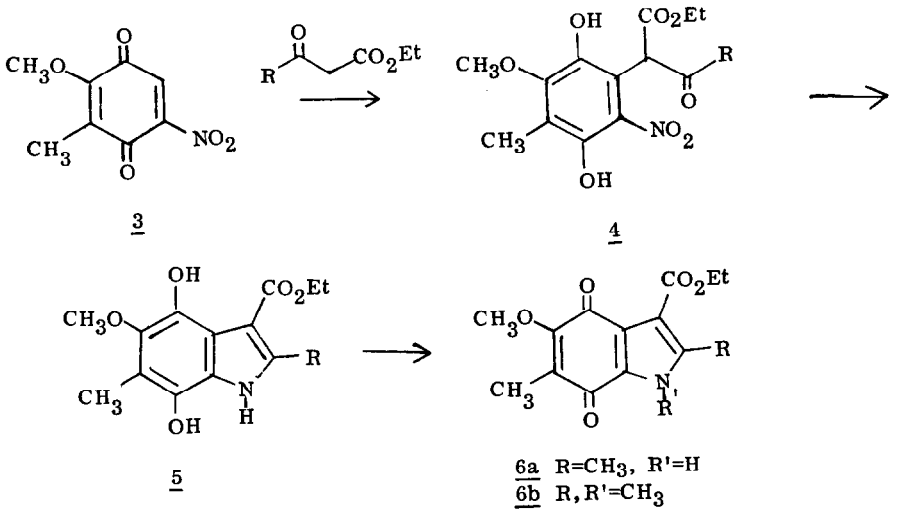


1b Mitomycin B



2

We wish to report the synthesis of the model indoloquinone 6a,[6-8] a compound which contains the complete D-ring functionality of the mitosenes. Our approach (Scheme 1) is based on the addition of an enol to the electron-deficient benzoquinone 3;[9] this approach should be easily extended to the convergent synthesis of more complex indoloquinones which might be elaborated to mitosenes.



3 4 5

6a R=CH_3, R'=H
6b R,R'=CH_3

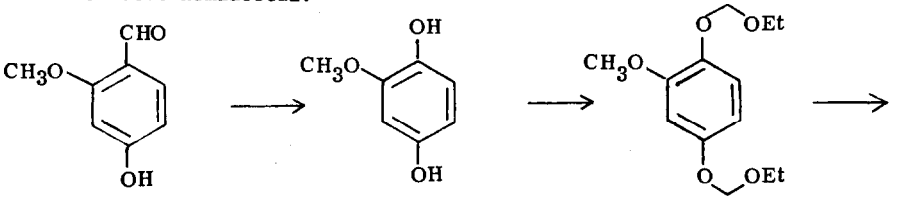
Scheme 1

Nitroquinones unsubstituted at the position β to the nitro group (e.g. 3) are expected to be very reactive Michael acceptors. Although a few examples of nitro-substituted quinones have been reported,[10] all but the parent nitrobenzoquinone are substituted at the β-position. In fact, nitrobenzoquinone is unstable and its reactions have not been studied.

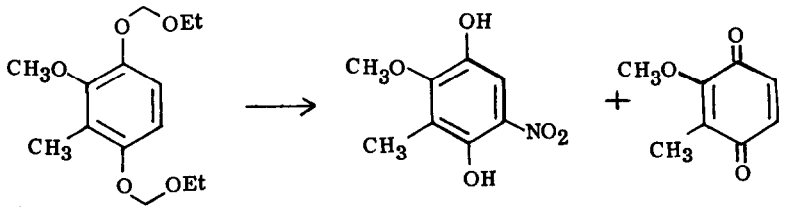
The non-nucleophilic conditions of Ag_2O oxidation of hydroquinone 11 seemed most appropriate for the production of nitroquinone 3. Hydroquinone 11 was prepared according to Scheme 2. Hydrogen peroxide converted vanillin to hydroquinone 8.[11] Treatment of 8 with sodium hydride followed by chloromethyl ethyl ether afforded the bis ether 9.[12,13] Lithiation and alkylation with methyl iodide converted 9 to 10.[12,14] Treatment of 10 with 90% nitric acid in acetic anhydride[15] gave a mixture from which 12% of quinone 12[16] could be recovered by distillation. Acid hydrolysis of the residue gave the desired hydroquinone 11, mp 137-138° in 19% yield.[12,17]

Treatment of hydroquinone 11 with Ag_2O in toluene containing anhydrous calcium sulfate[18] afforded a red solution. After stirring for one hour at room temperature, the reaction mixture was filtered under nitrogen and excess ethyl acetoacetate[19] was added. The reaction mixture was then stirred for two days under nitrogen at room temperature. Toluene and excess ethyl acetoacetate were removed under reduced pressure at room temperature and the residue was chromatographed on Merck silica gel. Elution with chloroform afforded 62% of a yellow crystalline adduct[17] ν(KBr) 3550, 1720, 1600 cm^{-1}, M^+ 327, which was homogeneous by tlc (mp 117-119° from ether).

The pmr spectrum ($CDCl_3$) of this material, (see below), suggests that it exists in the hemiacetal form 4a, which equilibrates in deuteriochloroform over two hours to a mixture (~2:1) of 4a and 4b, the stereoisomeric hemiacetal.



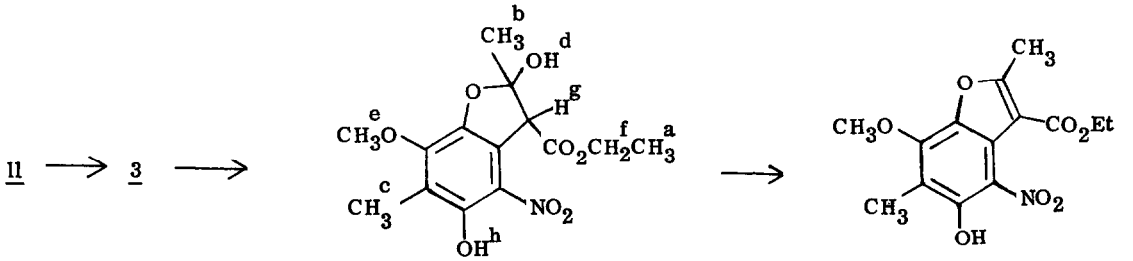
7 8 (90%) 9 (88%)



10 (92%) 11 12

Scheme 2

Treatment of 4 with gaseous HCl in ether gave the substituted benzofuran 13[12], in 79% yield.



4a 4b

	4a	4b
a	1.29,t,3H	———
b	1.84,s,3H	1.75,s
c	2.16,s,3H	———
d	3.77,s,1H	3.31,s exchange with D_2O
e	4.10,s } 5H	———
f	4.25,q }	———
g	4.63,s,1H	4.56,s exchange with D_2O, pyridine, overnight
h	10.98,s,1H	11.07,s exchange with D_2O

Hydrogenation of adduct 4 (10% Pd/C, EtOH, 1 atm) gave, after filtration, a colorless solution from which the air-sensitive indolohydroquinone 5, ν(KBr) 3280, 1600 cm^{-1}, δ(acetone-d_6) 1.38 (t)3H, 2.19(s)3H, 2.65(s)3H, 4.36(q)2H, and 10.61(s)1H, could be isolated by precipitation with chloroform. Oxidation of the alcoholic solution of the hydroquinone 5 (R=CH_3) with oxygen over 48 hours gave a red solution from which the crystalline indoloquinone 6a[17] could be isolated by concentration and preparative tlc (silica gel, $CHCl_3$:Et_2O::2:1). Recrystallization from CH_2Cl_2, pet. ether gave red crystals, 56% from 4, mp 214°, ν($CHCl_3$) 3490, 3210, 2910, 1695, 1665, 1625 cm^{-1}, δ($CDCl_3$) 1.33(t)3H, 1.88(s)3H, 2.51(s)3H, 4.04(s)3H, 4.30(q)2H, and 10.40(broad s)1H ppm, λ_{max}^{MeOH} 210 (log ε 4.27), 234 (4.11), 2.86(4.01) and 330 mμ (3.64).

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