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SYNTHETIC STUDIES ON MITOMYCINS. 1. A REGIOSPECIFIC MICHAEL ADDITION OF 2-METHYLCYCLOPENTANE-1,3-DIONE TO p-TOLUQUINONESULFONIMIDES.

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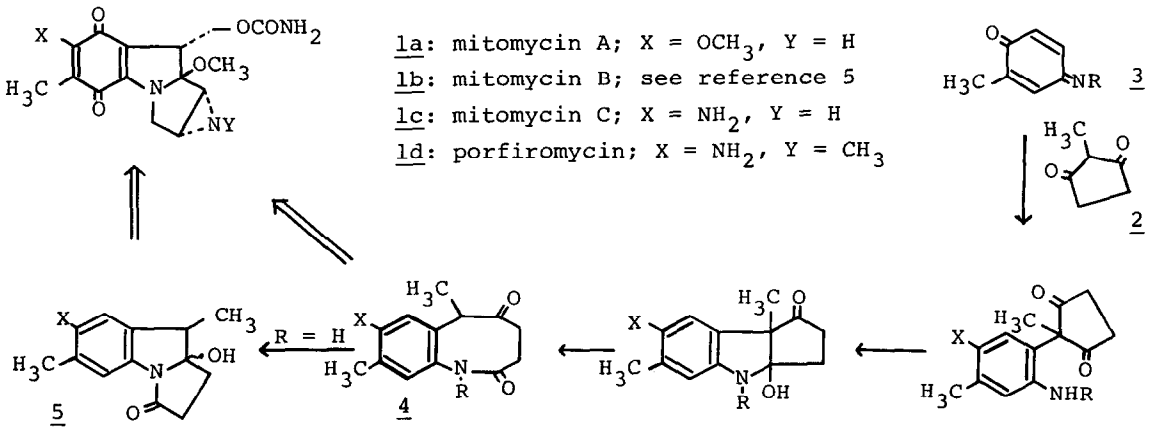
Summary: A Michael addition of 2-methylcyclopentane-1,3-dione to various p-toluquinone imides exclusively afforded the sole products in a regiospecific manner. Acid treatment of these adducts gave indole or benzofuran derivatives, which could be the key intermediates for synthesis of mitosane skeleton.

Mitomycins(1), the potent antitumor antibiotics, which contain several unique structural features including an aziridine group, were isolated in 1956.[1] Since their structures were elucidated in 1962,[2] numerous synthetic works have been reported.[3] Recently, Kishi and co-workers have described the first brilliant total syntheses of porfiromycin(1d), mitomycin A(1a) and mitomycin C(1c).[4] We had attempted another synthetic approach to these antibiotics as is shown in Scheme 1, for which purpose it was indispensable to create the new method to efficiently synthesize hydro-1-benzazocinone(4), because the so far known methods usually required multi-steps to furnish the eight-membered ring system with low over-all yields.

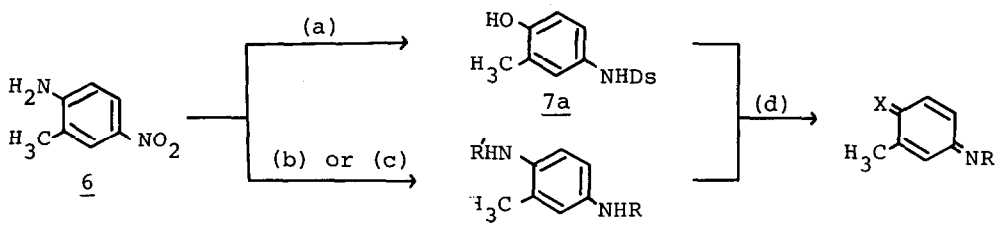
(Scheme 1)



1a: mitomycin A; X = OCH_3, Y = H
1b: mitomycin B; see reference 5
1c: mitomycin C; X = NH_2, Y = H
1d: porfiromycin; X = NH_2, Y = CH_3

The phenol 7a and sulfonamides 7b-d prepared by means of three methods (Scheme 2; (a), (b), and (c)) from an inexpensive reagent, 2-amino-5-nitrotoluene (6), were oxidized with lead tetraacetate[6] to give the four p-toluquinonesulfonimides 3a-d[7] in 47-69% yields from 6.

(Scheme 2)

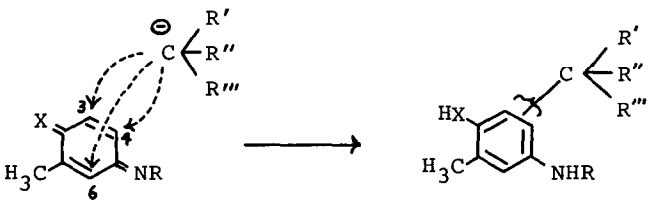


Ts = tosyl, Z = CO_2CH_2Ph
Ds = $SO_2N(CH_3)_2$

(a): 1) $NaNO_2$/aq. H_2SO_4/0°, then 130°. 2) H_2/Pd-C/CH_3OH. 3) DsCl/AcONa/acetone/reflux.
(b): 1) H_2/Pd-C/CH_3OH. 2) TsCl/pyridine.
(c): 1) TsCl/pyridine or DsCl/NaH/DMF. 2) H_2/Pd-C/CH_3OH. 3) Z-Cl/pyridine/CH_2Cl_2.
(d): 1) $Pb(OAc)_4$ /AcOH or CH_2Cl_2/room temperature.

In regard to the Michael addition of 2 to the above imides 3a-d, it is possible for the nucleophile to react with 3 at three positions(C_3, C_4, and C_6) (Scheme 3). Although C_6-position of the compound 3 could be hardly attacked due to the steric effect, it was difficult to predict whether C_3- or C_4-position should be predominantly attacked on account of both of steric effect and relative electron-density, as any information about the Michael reaction of various monosubstituted p-benzoquinonesulfonimides had not been provided.[6]

(Scheme 3)



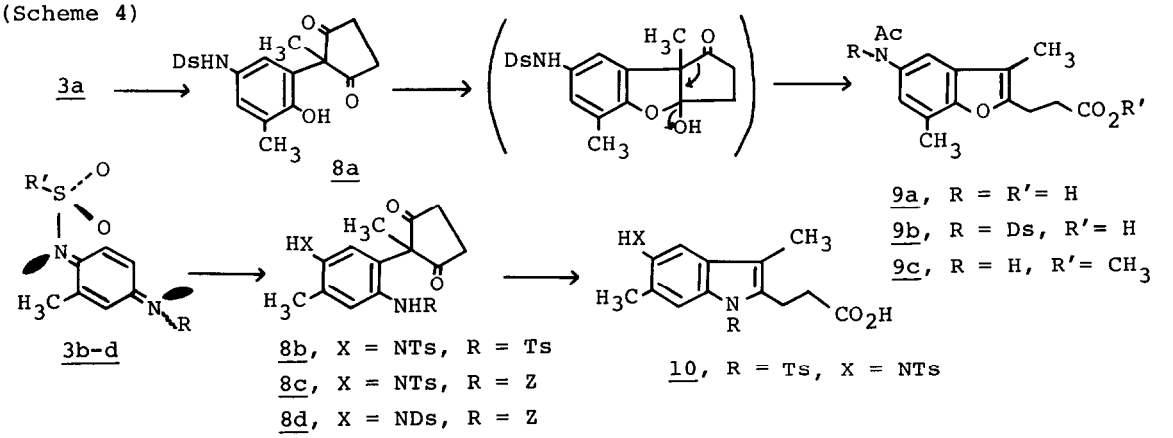
First of all, the monoimide 3a was subjected to the reaction with 2, in which 3 was added to a solution of 2 with 0.5 eq. of sodium methoxide at a room temperature to afford the adduct 8a in a quantitative yield.
To prove the structure of this compound 8a which could not be clearly established in this stage by its spectral data, the compound 8a was further cyclized under a condition at reflux with a large excess of sodium acetate in glacial acetic acid for 2 days to afford the benzofuran(9a, mp 212-3°, 49% yield) and (9b, resins, 33% yield).[7] Moreover, esterification of 9a with diazomethane gave 9c(mp 149° from CH_3OH), the structure of which was established by X-ray analysis.[8]

Secondly, reaction of 2 with the imide 3b under the same basic condition gave the adduct(8b, mp 202-4°, 100% yield) which was confirmed by physicochemical properties[ν(Nujol) 3450, 3250 and 1730 cm^{-1}; δ(DMSO-d_6) 1.02(s, 3), 2.05 (s, 3), 2.38(s, 6), 6.58(s, 1) and 7.11(s, 1) ppm; MS 540(M^+)].
To our surprise this result shows that the C_3-position covered with the big sulfonimide group in 3b is completely prevented from an attack of the nucleophile(Scheme 4).

Subsequently, the diimides 3c and 3d gave similarly the desired adducts (8c, mp 111-3°, 95% yield)[ν(Nujol) 3430, 1745 and 1690 cm^{-1}; δ($CDCl_3$) 1.25(s, 3), 2.07(s, 3), 2.39(s, 3), 5.35(s, 2) and 6.82(s, 1) ppm; MS 520(M^+)] and (8d, colorless oil, 86% yield)[ν($CHCl_3$) 3430, 3250, 1735 and 1690 cm^{-1}; δ($CDCl_3$) 1.40 (s, 3), 2.25(s, 3), 2.82(s, 6), 5.37(s, 2), 7.23(s, 1) and 7.25(s, 1) ppm; MS 473(M^+)], respectively.

Treatment of 8b with a large excess of sodium acetate in glacial acetic acid at reflux for 2 days gave the indole(10, mp 233-4°, 67% yield)[ν(Nujol) 3280, 1695 and 1595 cm^{-1}; δ(DMSO-d_6) 2.04(s, 3), 2.07(s, 3), 2.36(s, 3), 2.41(s, 3), 7.65(s, 1) and 7.81(s, 1) ppm; MS 540(M^+)] as a sole product, and in an attempt to cyclize 8b under other acidic or basic conditions yielded neither any cyclized products nor the compound 4 at all.

(Scheme 4)



The compounds[8c and 8c(R = Z)] can be easily converted to the corresponding free aminoketones[8c and 8d(R = H)], which will be further transformed into 5. These conversion will appear in the following communication.[9]

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7. Satisfactory elemental analyses and spectroscopic data were obtained for these substances.
8. We are grateful to Mr. T. Date, Analytical Center, Tanabe Seiyaku Co. Ltd., for his kind measurement of X-ray crystallography.
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