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A NEW SYNTHESIS OF PYRROLO[1,2-a]INDOLOQUINONE AND RELATED COMPOUND

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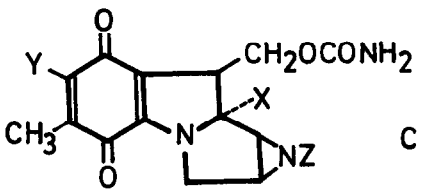
In the synthetic studies on mitomycin antibiotics (1), up to the present, a number of indoloquinones which lack the aziridino group or ring A have been prepared as mitomycin analogues.[1] In this paper we wish to describe a novel route to pyrrolo[1,2-a]indoloquinone and related compounds which seem to possess the same biological activities as those of mitomycin and the requisite skeleton for further elaboration.

Tosylhydrazone 3 (m.p. 242°) prepared from dihydroxyacetophenone 2 was oxidized with potassium nitrosodisulfonate in water - ethanol affording quinone 4 (decomp. 147-150°) in high yields (80-90%). On treatment with excess amines (pyrrolidine, piperidine and morpholine) in chloroform, 4 furnished aminoquinones 5 [5a, decomp. 124-125°; i.r. 3050 (>NH), 1670, 1660 (>C=O), 1528 (>N-C=C-C=O) cm^{-1}; n.m.r. ($CDCl_3$) δ 1.47-1.87 (4H, m, $-CH_2CH_2-$), 1.95 (3H, d, J = 1.8 Hz, $CH_3-C=C-H$), 2.03 (3H, s, $CH_3-C=N-$), 2.40 (3H, s, $-CH_3$), 3.12-3.54 (4H, m, 2 $-CH_2N<$), 6.40 (1H, q, J = 1.8 Hz, $H-C=C-CH_3$), 7.25 (2H, d, J = 8 Hz, aromatic proton), 7.80 (2H, d, J = 8 Hz, aromatic proton); 5b, decomp. 172-175°; 5c, decomp. 180-181°] in 70-80% yields, small amounts of sulfonamides 6 and, only in the case of 5c, indazoloquinone 7 (m.p. 170-172°).

Direct indoloquinone cyclization from 5 was examined by Bamford-Steven's method[2], but a intractable reaction mixture was resulted by the sensibility of quinone groups to base, and only a trace of indoloquinone 8 was obtained by silica gel chromatography. Many attempts were made to cyclize 5 to 8 changing reaction conditions. The mass spectrum of 5a did not show the molecular ion at m/e 401 but strongly at m/e 215 which agrees with the molecular weight of structure 8a. Moreover in g.l.c. 5 gave a very strong peak of 8. These facts suggest that thermal decomposition of 5 is expected to proceed in reaction course of the indoloquinone formation.

Heating 5a at 150° without a solvent for a few minutes, 8a was obtained in 37% yield. The structure of 8a was confirmed by the following spectral data: [m.p. 153-155°; i.r. 1640 (>C=O) cm^{-1}; n.m.r. ($CDCl_3$) δ 2.02 (3H, d, J = 1.8 Hz, $-CH_3$), 2.22 (3H, s, $-CH_3$), 2.50-2.70 (4H, m, $-CH_2CH_2-$),



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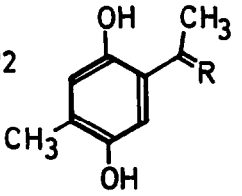
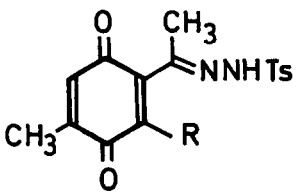
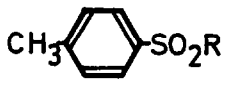


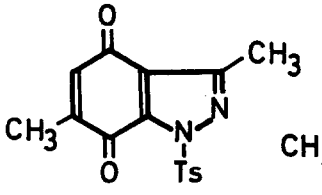
2 R = O
3 R = NNHTs



4 R = H
5a R = -N□
b R = -N⬡
c R = -N⬡O



6a R = -N□
b R = -N⬡
c R = -N⬡O



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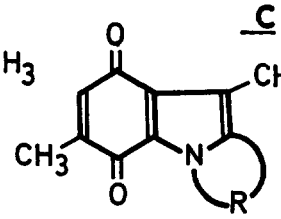
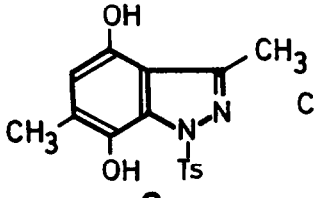


8a R = -(CH2)3-
b R = -(CH2)4-
c R = -(CH2)2OCH2-



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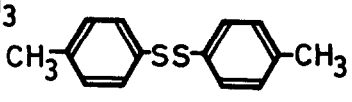

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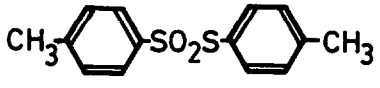

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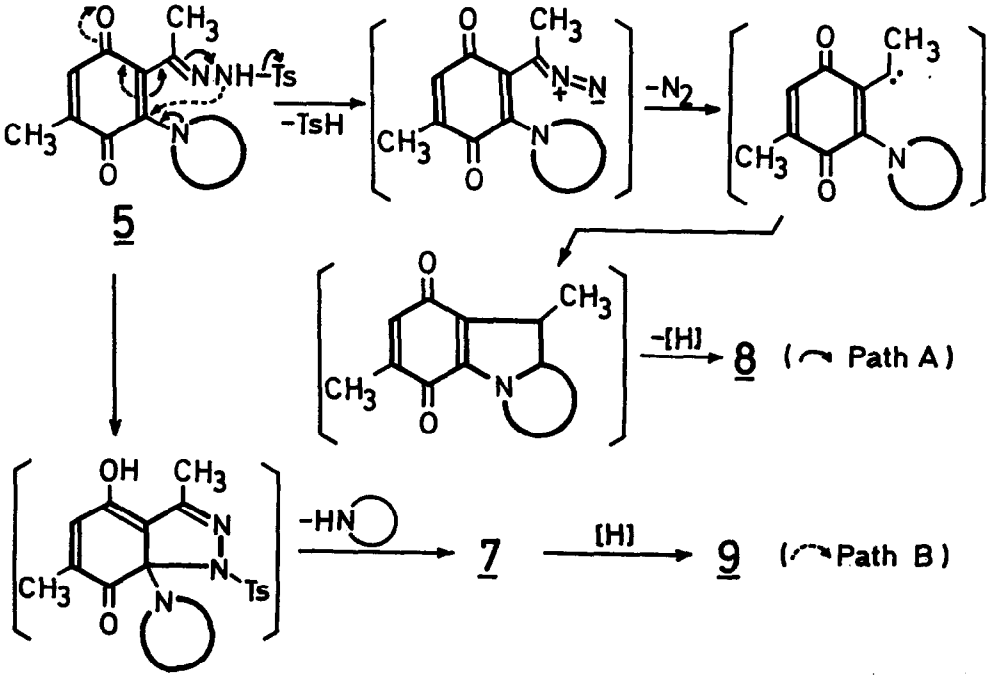
Table I

Starting Material compd. No.	Reaction conditions pyrolysis temperature	Yields of Reaction product (%) 6	7	8	9	10	11
5a	150°	—	—	37	8	9	2
5b	155°	—	—	15	trace	5	1
5c	180°	trace	2	7	trace	10	1

4.20 (2H, t, J = 7.5 Hz, $>NCH_2-$), 6.27 (1H, q, J = 1.8 Hz, $-CH=\overset{|}{C}-CH_3$); ms. m/e 215 (M^+).] Thermolysis of piperidino- 5b or morpholinoquinone 5c similarly gave 8b [m.p. 166-167°; i.r. 1638 (>C=O) cm^{-1}; n.m.r. ($CDCl_3$) δ 2.04 (3H, d, J = 1.8 Hz, $-CH_3$), 2.27 (3H, s, $-CH_3$), 4.23 (2H, t, J = 7.5 Hz, $>NCH_2-$), 6.30 (1H, q, J = 1.8 Hz, $-CH=\overset{|}{C}-CH_3$); ms. m/e 229 (M^+)] or 8c [m.p. 195-197°; i.r. 1639 (>C=O) cm^{-1}; n.m.r. ($CDCl_3$) δ 2.04 (3H, d, J = 1.8 Hz, $-CH_3$), 2.20 (3H, s, $-CH_3$), 3.90-4.50 (4H, m, 2 $>CH_2$), 4.80 (2H, s, $-CH_2O-$), 6.33 (1H, q, J = 1.8 Hz, $-CH=\overset{|}{C}-CH_3$); ms. m/e 231 (M^+)] as a major product. Disulfide 10, thiolsulfonate 11 and hydroxyindazole 9 [m.p. 191-193°, i.r. 3380 (-OH), 1349, 1162 ($>SO_2$) cm^{-1}; n.m.r. (CD_3COCD_3) δ 2.28 (3H, s, $-CH_3$), 2.38 (3H, s, $-CH_3$), 2.50 (3H, s, $-CH_3$), 6.59 (1H, s, aromatic proton), 7.35 (2H, d, J = 7.5 Hz, aromatic proton), 7.75 (2H, d, J = 7.5 Hz, aromatic proton), 8.58 (1H, s, -OH), 8.72 (1H, s, -OH, disappeared with D_2O); ms. m/e 332 (M^+)] were obtained as minor products in all these cases along with 8, but in the case of 5c small amounts of sulfonamide 6c and indazoloquinone 7 were also isolated. Reduction of 7 with sodium hydrosulfite in water - ethyl acetate afforded 9 in quantitative yield. The results are summarized in Table I.

Scheme I



To explain the above results, we propose such a mechanism that decomposition of aminoquinone 5 gives carbene intermediate, which undergoes further insertion and presumably intermolecular disproportionation to form indoloquinone 8 (Path A), and hydroxyindazole 9 via indazoloquinone 7 (Path B) as shown in Scheme I. The formation of disulfide 10 and thiolsulfonate 11 by the decomposition of toluenesulfinic acid [3] suggests the existence of the carbene as the reaction intermediate.

We believe that this thermal decomposition reaction may be of great utility in the simple synthesis of 1,2-disubstituted indoloquinones.

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