Synthesis of Indolequinones. New Synthetic Route to the Pyrrolo[1,2-*a*]indole Ring Systems

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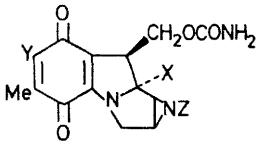
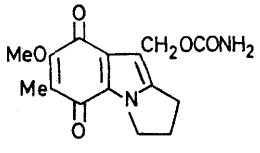
Summary The thermal decomposition of 2-azido-3-vinyl-1,4-quinones results in their smooth ring closure to indole-4,7-diones (indolequinones related to the biologically significant mitomycins)

THE mitomycins (**1**) are important naturally occurring antibiotic and antitumour agents. Several unsuccessful attempts to synthesise them have been made.[1–4] The Lederle group[2,3] have reported the synthesis of 7-methoxymitosene (**2**),[3] an analogue showing marked *in vivo* activity against gram-(+) bacteria, and the preparation of 1-substituted-7-methoxymitosenes has been described.[4] In these methods the quinone nucleus is constructed near the end of

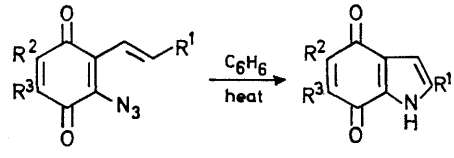


(1)



(2)

the sequence, a process involving transformations of low yields and selectivity. We report a new and general synthetic route to indolequinones starting with the quinone nucleus intact. The compound (**7**), a previously unknown naphthoquinone analogue of the mitosene ring system, was prepared by this method.

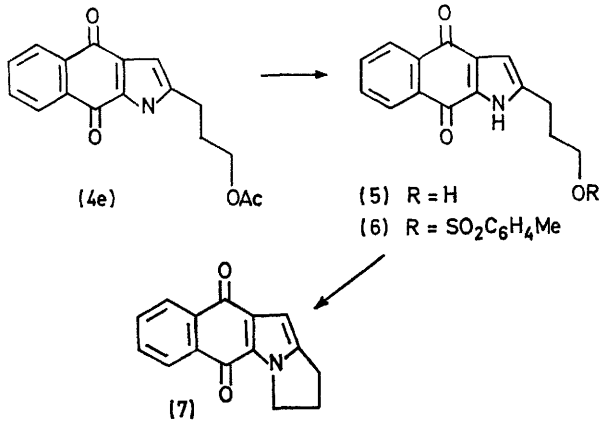


(3) (4)

	R^1	R^2 R^3	M.p.(°C)	Yield (%)
a	Me	/\	304–305	90
b	Pr	/\	211–212	81
c	$CH_2[CH_2]_8Me$	/\	154–155	76
d	Ph	/\	304–305	92
e	$CH_2CH_2CH_2OAc$	/\	181–182	88
f	Ph	Me Me	291–292	66

Thermolysis of the 2-azido-3-vinyl-1,4-quinones[5] (**3a—f**) in benzene under reflux results in their high yield (66—92%) transformation to the corresponding indolequinones (**4a—f**) which usually precipitate in high purity from the cooled reaction solution.

The structures of these new heterocyclic quinones are based upon their spectral (i.r., u.v., n.m.r.) and analytical data. Particularly characteristic are their i.r. absorptions for NH (3400 cm^{-1}) and quinone carbonyl (1675, 1645 cm^{-1}).



The thermal chemistry of the azidoquinones (**3a**—**f**) is different to that of 2-azido-3-alkyl (or aryl)-1,4-quinones, which ring contract to 2-cyano-4-cyclopentene-1,3-diones.[6] A precedent does exist for these ring closures, that of the thermal conversion of *o*-azidostyrenes into indoles.[7]

This method can be used for the conversion of (**4e**) into the pyrrolo[1,2-*a*]indole (**7**). Hydrolysis of (**4e**) in aqueous methanolic HCl under reflux gave the alcohol (**5**) in 94% yield (m.p. 214—216°). Treatment of the alcohol (**5**) with TsCl in pyridine gave the tosylate (**6**), m.p. 210—211°, in 57% isolated yield which upon reaction with potassium t-butoxide in Bu^tOH gave (**7**) in 88% yield [m.p. 188—189°; n.m.r. ($CDCl_3$) δ 2·33—3·07 (4H, m), 4·33 (2H, t, *J* 6·5 Hz), 6·41 (1H, s), 7·54—8·35 (4H, m)]. No attempt has yet been made to introduce the carbamoyloxymethyl group at C-9. However, this is not likely to be difficult since an analogous transformation was reported in the synthesis of (**2**) from 2,3-dihydro-7-methoxy-6-methyl-1*H*-pyrrolo[1,2-*a*]indole.[3]

This indolequinone synthesis is potentially the most versatile route to such compounds.[8] Azidoquinones are easily prepared[9] and there are several routes for the introduction of a vinyl group on the quinone nucleus.[5,10]

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