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1,3-DIPOLAR CYCLOADDITIONS TO OXIDOPYRAZINIUMS

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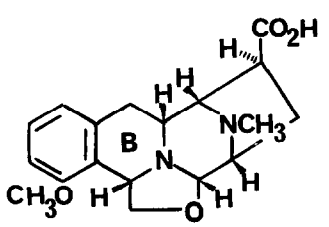
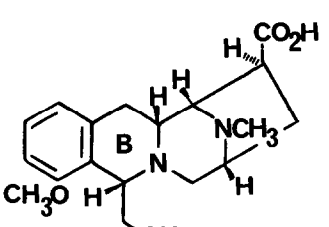
Abstract: 1,5-Dimethyl-3-oxidopyrazinium (6) undergoes cycloadditions with methyl acrylate,acrylonitrile, diethyl maleate, maleimide, methyl propiolate and diethyl acetylenedicarboxylate.

Quinocarcin (1) and quinocarcinol (2), antitumour metabolites isolated[1] from Streptomyces melanovinaceus, each contain a 3,8-diazabicyclo[3.2.1]octane nucleus, as does the hexacyclic, antibacterial, antitumour naphthyridinomycin (3), from S. pusitanus[2]. Considerable ingenuity


(1)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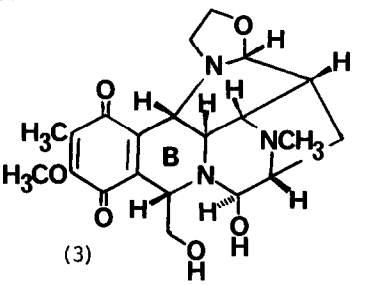
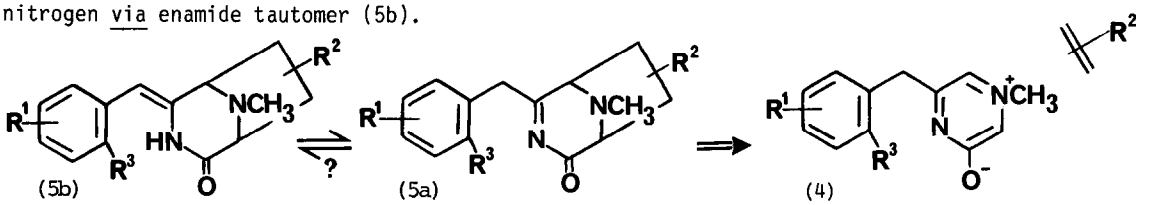
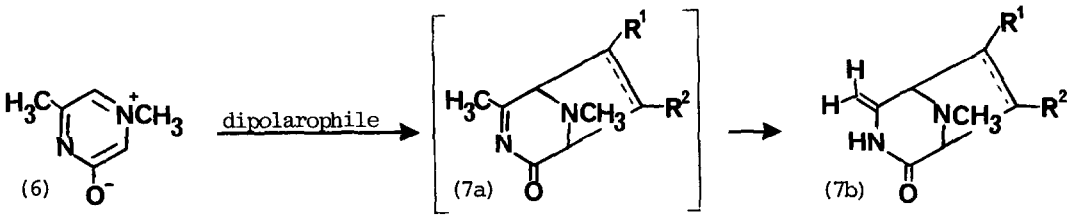

(3)

has been displayed in developing synthetic routes[3] to these compounds, but it seemed to us that cycloaddition of a suitable dipolarophile to an appropriate oxidopyrazinium, of the form (4), could provide a simple and effective entry to molecules (5), containing the required bridged bicyclic nucleus, carrying an oxygen substituent at the appropriate position, and having the potential both for closure of the B-ring (appropriate R^3) and introduction of the third nitrogen via enamide tautomer (5b).


(5b) (5a) (4)

In addition to the pioneering and extensive studies[4] by Katritzky et al. on cycloadditions to 3-oxidopyridiniums, a small number of comparable, or similar, cycloadditions to oxido- diaziniums has been reported[5]. It was pointed out[5c] at an early stage that the inclusion of an extra nitrogen in the heterocyclic ring reduces the tendency for dipolar cycloaddition so it is not surprising that all the known examples[5a-c,f] were, presumably, facilitated by having either an additional oxygen substituent, shown[6] to make additions in the pyridine series easier, or a fused benzenoid ring, and in agreement with this view, 1-methyl-3-oxido- pyridazinium itself and its 6-methyl-homologue were unreactive[5c] to a variety of ethylenic and acetylenic dipolarophiles. However, to be useful in the present context, it would be necessary for a simple 5-aralkyl-1-methyl-3-oxidopyrazinium (4) to undergo cycloaddition, and further, in the same regiochemical sense as that demonstrated by Katritzky for 3-oxidopyridiniums[4]; as a model for this we have now studied some reactions of 1,5-dimethyl-3-oxidopyrazinium (6).

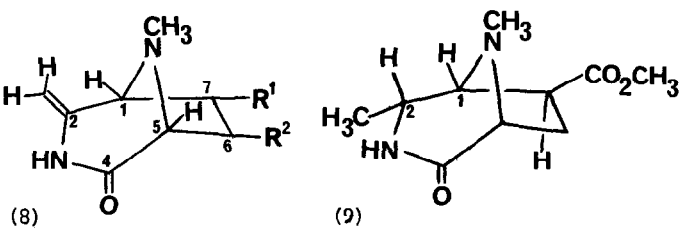
6-Methylpyrazin-2-one[7] was quaternised with iodomethane in refluxing ethanol and the resulting methiodide, m.p. 235°C, converted into zwitterion (6), m.p. 128-130°C, by treatment with triethylamine at room temperature. Dipolar cycloadditions of (6) with methyl acrylate, diethyl maleate, methyl propiolate, dimethyl acetylenedicarboxylate, maleimide and acrylonitrile were conducted in THF solution at room temperature or at reflux, in unoptimised yields between 25 and 58% (Table).



In all cases, the cycloadducts existed as enamide tautomer (7b), and not as the imine, initial (presumed) product (7a). Thus each had two, exocyclic methylene ^{1}H NMR singlet signals in the range δ4.2-4.4, and no C-methyl signal.

The regiochemistry of addition to methyl acrylate, to give (8a), was confirmed as that predicted by analogy with Katritzky's work[4], and required by the synthetic ambitions discussed above, by ^{1}H NMR analysis of the adduct and of its catalytic hydrogenation product (9). Of the two bridgehead proton signals from (8a), one, at δ3.98, was a singlet, showing it to be located on a carbon adjacent to a carbon carrying an exo-ester group, while that at δ3.52 was a doublet (J 7 Hz). That the carbon bearing the singlet bridgehead proton was also linked to the double bond carbon, C-2, not to the carbonyl carbon, C-4, which simple arguments based on the relative chemical shifts of the two bridgehead protons had suggested, was shown by the spectrum of the hydrogenation product (9)[8]. In this, the C-1-proton, now resonating at δ3.4, was coupled (J 7 Hz) to the newly introduced, methine proton, at C-2, incidentally demonstrating that addition of hydrogen had taken place from the exo-face of the six-membered ring.

(8)	R^1	R^2
a	exo-CO_2Me	H
b	exo-CN	H
c	endo-CN	H
d	exo-CO_2Et	exo-CO_2Et
e	CO_2Me (6,7-dehydro)	H
f	CO_2Et (6,7-dehydro)	CO_2Et
g	exo-CH.CO.NH.CH-exo	



In reaction with acrylonitrile, both exo- (8b) and endo-nitrile (8c) isomers were obtained in approximately equal proportions, the regiochemistry of addition following from spectroscopic analogy with the acrylate adduct. Noting the presence of endo adduct in this case, the question arose as to whether, at lower temperature, reaction with methyl acrylate might produce the endo isomer, however although cycloaddition proceeded just as smoothly at room temperature, the alternative isomer could not be detected.

This work has demonstrated the ease, in comparison with the closest literature precedent[5c], with which a simple 3-oxidopyrazinium undergoes cycloaddition, across carbons 2 and 6, with a variety of dipolarophiles. The regiochemistry of addition of unsymmetrical alkenes and the isolation of both endo and exo isomers (8b and c) make the results a firm basis for the current further development of a synthetic route to quinocarcinol and related substances.

Experimental

1,5-Dimethyl-3-oxidopyrazinium (6). - 6-Methylpyrazin-2-one methiodide[9] (0.8 g), suspended in dry MeOH (10 ml), was treated with Et_3N dropwise during 3 min with vigorous agitation; a homogeneous solution resulted. After 2 h at room temperature the mixture was filtered, the filtrate reduced in volume by a half and applied to a column of silica. The methanol eluate was evaporated and the resulting zwitterion[9] used without further purification.

Typical cycloaddition. - The zwitterion (6) (0.1 g) was suspended in dry THF (10 ml) and reacted with 6-9 mol equivalents of the dipolarophile at room temperature or at reflux for 1-3 h. The solvent and excess reactant were removed under vacuum and the residue purified by chromatography.

Table[9]

Dipolarophile (mol equivs)	Product(s)	°C/h	Isolated yield pure product	m.p.(°C)	Crystallised from
Methyl acrylate (8)	(8a)	reflux/1	51	118	n-C_6H_{14}/THF
Acrylonitrile (8)	(8b)	20/3	25	180.5-182	MeOH
	(8c)		22	147-148.5	n-C_6H_{14}/THF
Diethyl maleate (9)	(8d)	reflux/2.5	35	121-123	n-C_6H_{14}/THF
Methyl propiolate (8)	(8e)	reflux/1.5	58	100-101	n-C_6H_{14}/THF
Dimethyl acetylene dicarboxylate (6)	(8f)	20/1.5	40	118-120	n-C_6H_{14}/THF
Maleimide[10] (6)	(8g)	20/3	25	250	MeOH

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8. m.p. 129-131°C.[9] Hydrogenation of (8a) proceeded in EtOH solution over 5% Pd/C at atmospheric temperature and pressure.

9. All new compounds gave satisfactory combustion analyses and spectroscopic data consistent with the structures assigned.

10. Since this dipolarophile could not be removed by evaporation, the product was isolated by Soxhlet extracting excess maleimide with Et_2O; the cycloadduct was very sparingly soluble in Et_2O.

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