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REACTIONS OF THE PYRROLIDINE DIENAMINE OF PUMMERER'S KETONE WITH NITROSOCARBONYLMETHANE

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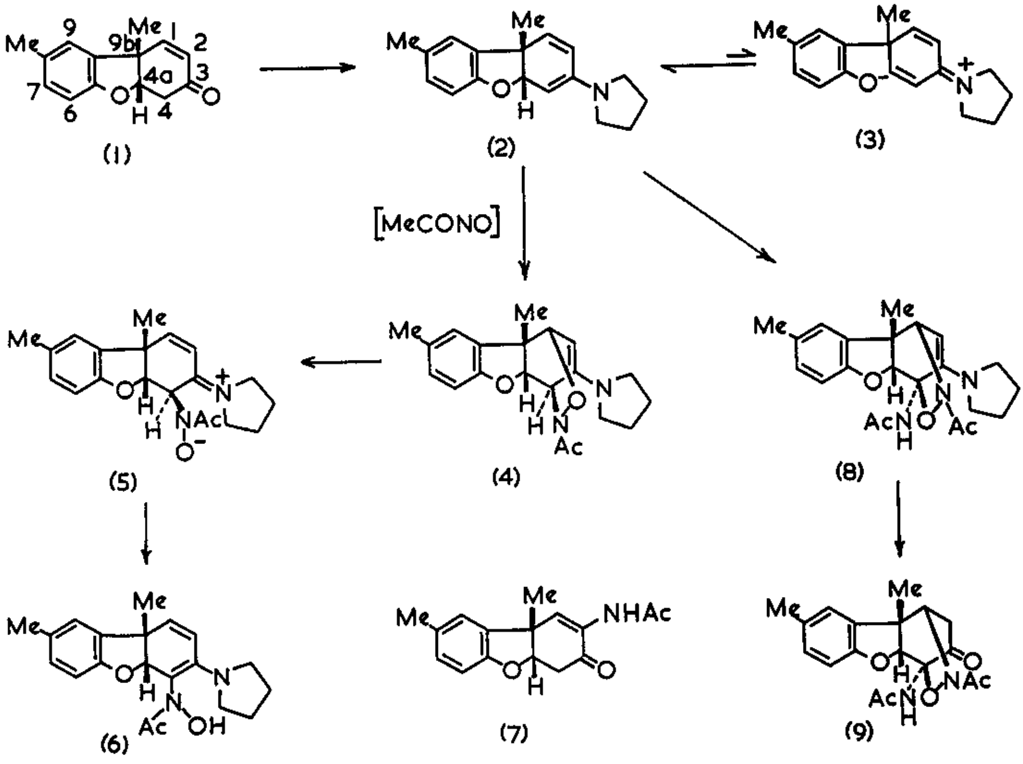
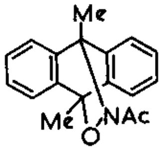
Abstract - The pyrrolidine dienamine (2) of Pummerer's ketone (1) reacts with the dienophile nitrosocarbonylmethane to give a bridged oxazine (9). The structure (9), incorporating 2 mol equiv. of the nitroso compound with reductive loss of 1 oxygen atom, has been determined by X-ray methods. Other products were the hydroxamic acid (6) and the acetamidoenone (7).

Barton and his coworkers[1] proposed the constitution (1) for Pummerer's ketone, an oxidation product[2] of *p*-cresol, and, on structural and mechanistic grounds, formulated[3] the oxidative coupling of phenols as a general biogenetic theory. This has withstood the test of numerous biosynthetic experiments and has formed the basis for the total synthesis of phenolic natural products following 'biomimetic' routes. Pummerer's ketone [the racemic form of (1)] has more recently been employed[4] as a 'pharmacophoric synthon' for the synthesis of analogues of the morphine alkaloids. We selected the pyrrolidine dienamine (2)[5] of Pummerer's ketone to extend our study[6] of the Diels-Alder reactions of acylnitroso compounds (RCONO), a class of transient dienophiles formed by oxidation of hydroxamic acids (RCONHOH)[7].

The ^{1}H nmr spectrum (100 MHz) of the dienamine (2), in deuteriochloroform at ambient temperature, showed broad, ill-defined signals for 1-, 2-, 4-, and 4a-H, in agreement with literature reports[5]. Confirmation that signal broadening arose from site exchange, presumably *via* the transformation (2) $\rightleftharpoons$ (3), was obtained from variable temperature studies. At -60°C the spectrum showed a pair of AB quartets, δ 6.12 and 5.74 (*J* 10 Hz, 2- and 1-H), and δ 5.09 and 4.40 (*J* 6 Hz, 4a- and 4-H), as expected for the dienamine structure (2). With increasing temperature, the signals broadened and merged and at 60°C had coalesced to form a broad singlet, δ 5.34.

The dienamine (2) reacted with nitrosocarbonylmethane (MeCONO) formed *in situ* from acetohydroxamic (MeCONHOH) under the usual conditions.[6] Thus, acetohydroxamic acid (2 mol equiv.) was added slowly to the dienamine (2) and tetraethylammonium periodate (2 mol equiv.) in dichloromethane at 0°C. Chromatography of the reaction mixture gave, as a major crystalline product (28%), the oxazine (9), presumably derived from the enamine (8) by hydrolysis. Many structural features of this product (9) were revealed spectroscopically. However, the elemental composition implied the


Me
9
9b
Me
1
2
4a
3
7
6
4
H
O
(1)
(2)
(3)
[MeCONO]
(4)
(5)
(6)
(7)
(8)
(9)
NHAc
AcN
NAc
Ac
N
O⁻
OH


Me
Me
NAc
O

(10)

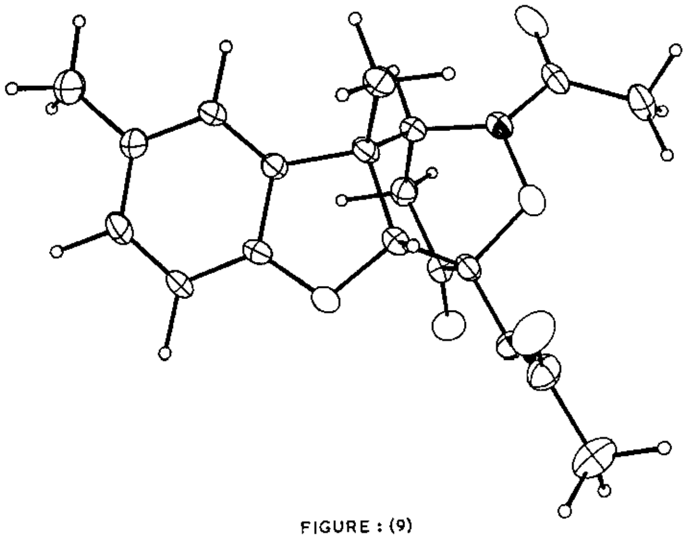


FIGURE : (9)

incorporation of 2 mol equivalents of nitrosocarbonylmethane with, remarkably, reductive removal of 1 oxygen atom under oxidising conditions. Moreover, the ir spectrum showed a carbonyl band with an unexpectedly high frequency, $_{\text{max.}}$ (CCl$_4$) 1750 cm^{-1}. The structure (9) was elucidated by X-ray crystallography (see Figure). A similar product (9; Ac = Bz), $\nu_{\text{max.}}$ (CCl$_4$) 1750 cm^{-1}, was obtained from the dienamine (2) and nitrosocarbonylbenzene formed in situ from benzohydroxamic acid.

In order to clarify the mechanism of formation of the bridged oxazine (9), the dienamine (2) was again treated with nitrosocarbonylmethane, this time released slowly by retro-Diels-Alder cleavage of the 9,10-dimethylanthracene adduct (10)[8]. Thus, the dienamine (2) and the adduct (10) (2 mol equiv.) were heated in benzene at 60°C for 27 h. Chromatography of the reaction mixture gave Pummerer's ketone (1) (24%), presumably derived by hydrolysis of the dienamine (2), the oxazine (9) (14%), and 2 new crystalline products, the hydroxamic acid (6) (18%) and the acetamidoenone (7) (4%). The hydroxamic acid (6) may arise from the reaction sequence (2) → (4) → (5) → (6). Also, attachment of the acetamido group at C-2 rather than C-4 in the enone (7) may result from opening and reclosure of the benzofuran ring in either a dienamine [cf. (2) ⇌ (3)] or enone[9] derivative. However, two products, (7) and (9), had again undergone reductive deoxygenation.

Initially, the hydroxamic acid (6) was thought likely to be a precursor for the other two products. However, this hydroxamic acid (6) was recovered in good yield after treatment, under the usual conditions, either with acetohydroxamic acid and tetraethylammonium periodate or with the adduct (10). *Experiments are in progress with other* C-nitroso compounds in order to clarify the reaction mechanisms, in particular the unaccounted loss of oxygen.

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PHYSICAL DATA FOR NEW COMPOUNDS

Compound (6): mp 166–168°C (from Et$_2$O-light petroleum); $\nu_{\text{max.}}$ (CHCl$_3$) 3385, 1678, and 1488 cm^{-1}; δ_H (100 MHz; CDCl$_3$) 1.68 (7H, m, 9b-Me and pyrrolidinyl 3- and 4-CH$_2$), 2.14 (s, Ac), 2.28 (s, 8-Me), 2.2–3.0 (4H, m, pyrrolidinyl 2- and 5-CH$_2$), 5.93 (d, J 10.0 Hz, 2-H), 6.06 (d, J 1.8 Hz, 4a-H), 6.48 (dd, J 10.0 and 1.8 Hz, 1-H), 6.70 (d, J 8.4 Hz, 6-H), 7.00 (2H, m, 7- and 9-H), and 7.17 (br s, OH).

Compound (7): mp 167–168°C (from Et$_2$O-light petroleum); $\nu_{\text{max.}}$ (CHCl$_3$) 3385, 1675, and 1510 cm^{-1}; δ_H (100 MHz; CDCl$_3$) 1.60 (s, 9b-Me), 2.04 (s, Ac), 2.30 (s, 8-Me), 2.86 (dd, J 17.7 and 3.7

Hz, 4-H), 3.16 (dd, *J* 17.7 and 2.9 Hz, 4-H), 4.58 (ddd, *J* 3.7, 2.9, and 1.7 Hz, 4a-H), 6.68 (d, *J* 8.0 Hz, 6-H), 6.95 (br d, *J* 8.0 Hz, 7-H), 7.05 (br s, 9-H), 7.44 (d, *J* 1.6 Hz, 1-H), and 7.73 (br s, NH, exch. with D_2O).

Compound (9): mp 192-193°C (from CH_2Cl_2-light petroleum); $\nu_{max.}$ (CCl_4) 3480, 1750, 1708, and 1665 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 1.65 (s, 9b-Me), 2.13 (s, ONAc), 2.15 (s, NH*Ac*), 2.26 (s, 8-Me), 2.32 (dd, *J* 19.5 and 1.9 Hz, 2-H), 2.70 (dd, *J* 19.5 and 3.9 Hz, 2-H), 5.10 (m, 1-H), 5.98 (s, 4a-H), 6.63 (d, *J* 8.2 Hz, 6-H), 6.85 (br s, NH, exch. with D_2O), 6.90 (m, 9-H), and 6.95 (dm, *J* 8.2 Hz, 7-H); δ_C (50.4 MHz; $CDCl_3$) 20.2 (9b-Me), 20.75 (8-Me), 24.3 (CO*Me*), 24.5 (CO*Me*), 39.1 (C-2), 49.0 (C-9b), 54.2 (C-1), 83.5 (C-4a), 86.0 (C-4), 110.2 (C-6), 123.7 (C-9), 129.6 (C-8 or -9a), 130.5 (C-7), 131.9 (C-9a or -8), 156.3 (C-5a), 169.5 (*C*OMe), 170.3 (*C*OMe), and 197.45 (C-3); *crystal data*: $C_{18}H_{20}N_2O_5$, *M* = 344.4, triclinic, space group $P\bar{1}$, *a* = 9.890(1), *b* = 11.789(2), *c* = 16.969(4) Å, α = 74.63(2), β = 77.33(2), γ = 74.74(1)°, *U* = 1816.5 $Å^3$, *F*(000) = 728, D_C = 1.26 g cm^{-3}, *Z* = 4, μ(Mo-*K*α) = 0.93 cm^{-1}. 2428 Independent reflections ($I \geqslant 3.0\sigma_I$) were measured on an Enraf-Nonius CAD-4 automatic diffractometer. The structure was solved by MITHRIL[10] using direct techniques and refined to a final *R* value of 0.087. There are two independent molecules in the asymmetric unit.

Compound (9; Ac = Bz): mp 186-188°C (from CH_2Cl_2-light petroleum); $\nu_{max.}$ (CCl_4) 3385, 1750, 1688, and 1640 cm^{-1}; δ_H (90 MHz; $CDCl_3$) 1.84 (s, 9b-Me), 2.28 (s, 8-Me), 2.42 (dd, *J* 19.5 and *ca.* 2 Hz, 2-H), 2.94 (dd, *J* 19.5 and *ca.* 4 Hz, 2-H), 5.28 (m, 1-H), 6.41 (s, 4a-H), 6.63 (d, *J* 8 Hz, 6-H), 6.98 (2H, m, 7- and 9-H), 7.45 (m, *m*- and *p*-Bz-H), and 7.86 (m, *o*-Bz-H).

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