REACTION OF PYRIDINE 1-OXIDE WITH METHYL PROPIOLATE: A PYRIDO-OXEPINE AND OTHER NOVEL PRODUCTS†

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Abstract- The title reaction is much more complex than those of pyridine 1-oxides with other activated acetylenes. Eight products have been isolated and five characterized: 4-8. The most interesting is a pyrido-oxepin 8 whose structure has been firmly established by single crystal X-ray analysis. The main products thus result from reaction of 3 moles of methyl propiolate with one mole of pyridine 1-oxide. The 1:1 (6) and 1:2 (7) adducts are very minor products.

The alkylation of pyridine 1-oxides and related compounds with activated acetylenes has uncovered a number of novel rearrangements of heteroaromatic N-oxides,[1] including 1,3-, 1,5-, 3,5- and consecutive 3,5-shifts. The latter resulted in the formation of furo[3,2-c]pyridines.[2] A 1,2-adduct was obtained as a minor product from the reaction with phenylcyanoacetylene and a 3-pyridyl divinyl ether structure (1) assigned to it. As far as we know the reaction of pyridine 1-oxide (2) with activated acetylenes bearing only one substituent has not been reported[3] and we now describe its behavior towards methyl propiolate (3) and the unusual results obtained.

When equimolar amounts of 2 and 3 were first boiled under reflux in benzene for 30h two products, 4 and 5, were isolated in approximately 20% total yield. Both had molecular formulae corresponding to the addition of 3 molecules of 3 to one of 2, with loss of a CHO fragment. Heating 2 and 3 (1:3 molar ratio) in DMF at 90°C gave 4 (17.9%) and 5 (22.6%). Subsequent repetition of the benzene solution work by a different coworker showed that actually five compounds could be isolated and characterized; three more were formed but in amounts too small to permit identification. Table 1 summarizes the results.

The simplest product (6)(2.3%), mp 145-146°C, was obtained when a 3-fold excess of 2 relative to 3 was used. It was readily characterized on the basis of its analysis and spectral data (mass, ^{1}H and ^{13}C NMR, IR)[δ17.5 (br s, NH), 9.66 (s, CHO), 8.66 (J = 8.8 Hz), 7.91 (m), 7.88 (dd, J = 7.1, 1.7 Hz), 7.02 (dt, J = 7.1, 1.2 Hz)(ring protons); $\nu_{C=O}$ 1710, 1645 cm^{-1}], the latter suggesting

†Dedicated to Prof. Gilbert Stork in honor of his 65th birthday.

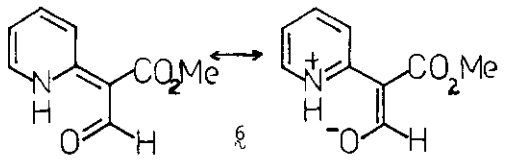
TABLE 1. Reaction of pyridine 1-oxide (2) with methyl propiolate (3) in benzene

Molar ratio 2:3	temp. °C	time h	products % [a] 4	5	6	7	8	9	not characterized
1:1	refl.	30	14.8	6.0					
1:3	refl.	30	2.1	6.0			2.5	4	
1:3[b]	90	10	17.9	22.6					
3:1	refl.	43	1.6	3.6	2.3	8.0	2.6	1.6	
3:1	45	69	1.2	5.0			5.4		yellow solid, mp 184-185°C, m/e 347, $C_{17}H_{17}NO_7$, (0.5%)
1:3	50	88	3.3	4.0			1.6		pink solid, mp 170-172°C, m/e 261, $C_{13}H_{11}NO_5$, (0.08%)

[a] Yields calculated on basis of reactant present in smallest amount.

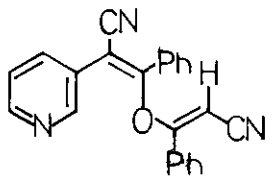
[b] In DMF solution.

some contribution of the dipolar aromatic form to the structure:



6

Under these conditions, the main product (8.0%) isolated was 7, mp 142-143°C, a 1:2 adduct. In principle, two structures could fit the data: 7 (analogous to 1 above) and 7a. Structure 7 is preferred on the basis of the NMR data [δ8.58 (br, H_2, H_6), 7.68 (dt, $J_{4,5}$ = 7.9 Hz, $J_{4,6}$ = $J_{2,4}$ = 2Hz, H_4), 7.32 (dd, $J_{4,5}$ = 7.9 Hz, $J_{5,6}$ = 5.0 Hz, H_5) which indicate a pyridine rather than a pyridinium structure (see also ref. 6 below).



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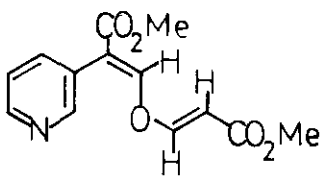

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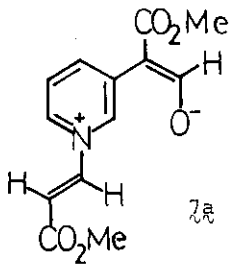


7a

The most interesting product proved to be 8, yellow crystals, mp 148°C, "best" formed (5.4%) from 2:3 = 3:1 in benzene at 45°C for 69h. Its molecular formula corresponded to a 3:1 adduct of acetylene to N-oxide. When it was heated in the presence of pyridine 1-oxide it gave small amounts of 4 and 5 with loss of CHO fragment. The same result (but with lower yields) was obtained without addition of 2. NMR spectroscopy indicated the absence of a formyl group in 8.[4] The structure was unambiguosly established by single crystal X-ray analysis and one view is given

in Fig. 1.[5] This seems to be the first recorded example of a pyrido-oxepin derivative.

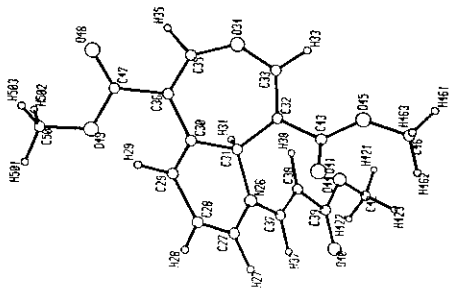
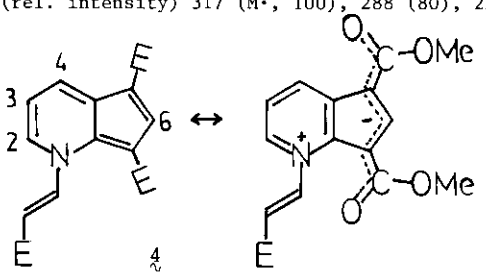


Figure 1. ORTEP diagram of 1:3 adduct 8.

The structure proposed for 4 (orange-red solid, mp 199-200°C), is based on its microanalysis and spectral properties. Aromatic canonical forms may be major contributors since the pyridine α-proton appears at lower field (δ 8.89, dd, $J_{2,3}$ = 7.6, 0.7 Hz) than expected for a neutral pyridine, indicating a pyridinium ion. Also, the acrylate proton β- to the carbonyl appears at lower field (δ 9.69, $J_{\alpha,\beta}$ = 13.7 Hz) than calculated[6] for the corresponding acrylate proton at a carbon bearing an $NR_{conj.}$ group (δ_{calc} 8.73). It seems more likely, however, that the ester at C_7 plays the major role here by deshieding H_β appreciably (see 5 below). The other spectral data also fit this structure [δ 8.38 (s, 1H, H_6), 7.90 (d, 1H, $J_{3,4}$ = 6.4 Hz, H_4), 7.12 (t, 1H, $J_{2,3}$ = 7.3 Hz, $J_{3,4}$ = 6.4 Hz, H_3); IR (KBr) 1740, 1715, 1685, 1670, 1630 cm^{-1}; mass spectrum (70eV) m/e (rel. intensity) 317 (M^+, 100), 288 (80), 259 (10)].



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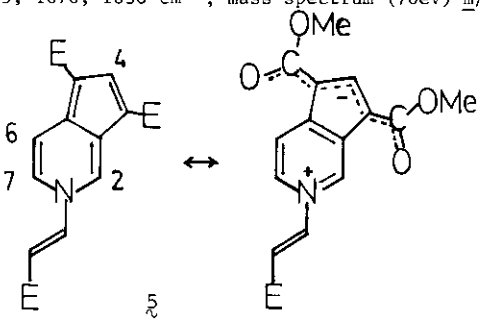

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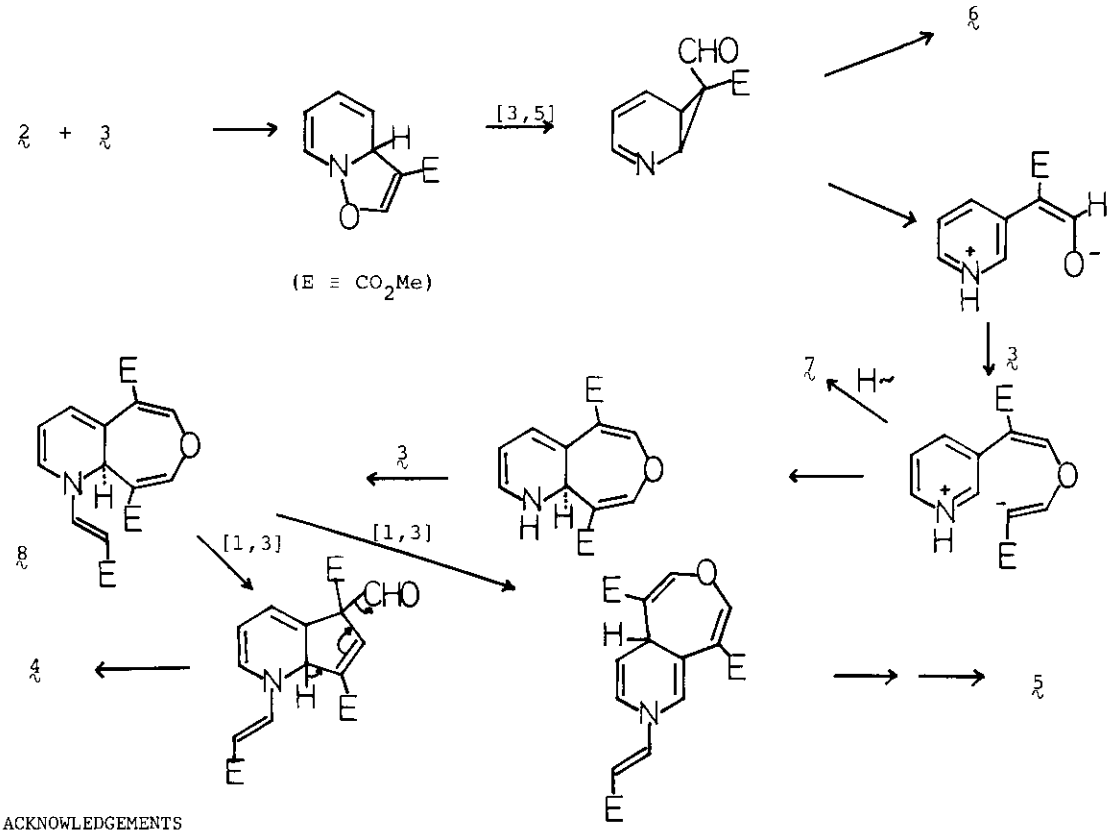
On a similar basis,[7] compound 5 (yellow solid, mp 206-207°C) was also assigned the structure shown (note that H_β is not subject to deshielding by CO_2Me and resonates near the calculated value).

The formation of products 4, 5, 6, 7, and 8 may be tentatively accounted for as in the Scheme. Benzo-oxepin is known[8a] to undergo acid-catalyzed isomerization to indene-3-carboxaldehyde, while dihydro-oxepin gives cyclopentene-1-carboxaldehyde.[8b] Alternative mechanisms are clearly possible e.g. involving the addition of 2 to 8 followed by ring-opening and recyclization with or without migration. Further work is necessary to establish the mechanism(s), and the structure of 9 ($C_{25}H_{24}N_2O_6$, mp 248°C), corresponding to the addition of 4 molecules of 3 to 2 of 2 with elimination of (CH_2O_2), as well as of the two other uncharacterized products mentioned in Table 1.

SCHEME



ACKNOWLEDGEMENTS

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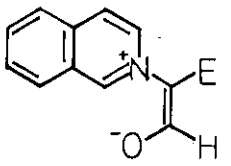
2. R. A. Abramovitch and I. Shinkai, J. Am. Chem. Soc. 1975, 97, 3227.

3. The reaction of isoquinoline-N-oxide with 3 (1:1 molar ratio) has been reported to give a good yield of the N-ylide (A) (R. Huisgen, H. Seidl, and J. Wulff, Chem. Ber. 1969, 102, 915) and this has been confirmed (R. A. Abramovitch and I. Shinkai, unpublished results and present work). When three equivalents of 3 are used a 1:3 adduct (microanalysis) can also be isolated in low yield as a red solid, mp 193-194°C, whose NMR spectrum indicates the presence of an acrylate function (δ 6.91, 5.37, J = 14 Hz).

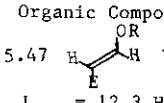


(A)

4. 8: ^{1}H NMR ($CDCl_3$) δ 7.49 (s, 1H), 7.43 (d, 1H, $J_{\alpha,\beta}$ = 13.8 Hz H_β), 7.31 (d, 1H, J = 2Hz), 6.40 (d, 1H, J = 6.1), 6.34 (d, 1H, J = 7.0 Hz), 5.44 (brd, 1H, J = 2 Hz), 5.36 (dd, 1H, J = 6.1, 7.3 Hz), 4.98 (dd, 1H, $J_{\alpha,\beta}$ = 13.6 Hz, J = 0.65, H_α), 3.78 (s, 3H), 3.70 (s, 3H), 3.69 (s, 3H); m/e (rel. int.) 347 (M^+, 82), 330 (100), 318 (15), 316 (25), 302 (13), 288 (68).

5. $C_{17}H_{17}NO_7$, MW 347.32, F(000) = 728. Triclinic, a = 13.064(3), b = 12.262(3), c = 11.183(3), α = 93.06(2), β = 78.99(2), δ = 110.71(2), V = 1645Å^3, space group $P\bar{1}$, Z = 4. D_m = 1.42 g.cm^{-3}, D_x = 1.402 g.cm^{-3}. 2θ-ω scan was used with 40 steps of 0.03°. Three standard reflections were measured every 50 reflections and not significant drop in intensity was observed. 4813 intensities were measured for θ≤56°, from which 1993 unique intensities were obtained after Lorenz and polarization corrections and merging. 234 reflections with I<2.σ(I) were considered as unobserved. The final R value for 1759 observed reflection was 6.0%.

6. F. Scheinmann, Ed., "An Introduction to Spectroscopic Methods for the Identification of Organic Compounds", Vol 1. Pergamon Press, Oxford, 1970, p. 64. The values calculated for



also support proposed structure 7 over 7a (Found: δ7.67 (H_β), 5.63 (H_α), $J_{\alpha,\beta}$ = 12.3 Hz).

7. 5: ^{1}H NMR (DMSO-d_6) δ9.34 (br s, 1H, H_2), 8.54 (d, 1H, $J_{\alpha,\beta}$ = 14.4Hz, H_β), 8.50 (dd, 1H $J_{6,7}$= 6.3 Hz, $J_{2,7}$ = 1.5 Hz, H_7), 8.08 (d, $J_{6,7}$ = 6.3 Hz, H_6, deshielded by CO_2Me at C_5), 8.04 (s, 1H, H_4), 6.88 (d, 1H, $J_{\alpha,\beta}$ = 14.4 Hz H_α); IR (KBr) 1740, 1695,1670, 1620 cm^{-1}; mass spectrum (70eV) m/e (rel. intensity) 317 (M^+, 89), 286 (100).

8. (a) K. Dimroth, G. Pohl, and H. Follman, Chem. Ber. 1966, 99, 634.
(b) G. Pohl, Dissertation, University of Marburg, 1961 (quoted in "Houben-Weyl Methoden der organischen Chemie", (E. Mueller, Ed.), Vol. 6/4, Georg Thieme Verlag, Stuttgart, 1966, p. 466).

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