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UNSATURATED HETEROCYCLIC SYSTEMS—XVI[1]

A NOVEL SYNTHESIS OF CYCLIC HYDROXAMIC ACID ESTERS

L. A. PAQUETTE[2]
Department of Chemistry, The Upjohn Company, Kalamazoo, Michigan[3]

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Abstract—The formation of O-substituted derivatives of 1-hydroxy-2(1H)-pyridone and 1-hydroxycarbostyril (cyclic hydroxamic acid esters) on treatment of 2-ethoxypyridine-1-oxide and 2-ethoxyquinoline-1-oxide monohydrate, respectively, with primary and secondary halides is described. The interaction of 4-ethoxypyridine-1-oxide and benzyl halides under similar conditions afforded only the corresponding benzaldehydes. The mechanisms of these reactions are discussed.

THE ready conversion of 2-alkoxypyridines and 2-alkoxyquinolines to N-substituted-2(1H)-pyridones and -carbostyrils, respectively, under conditions of attempted quaternization with alkyl halides has been utilized with passing interest by several groups of workers.[4–8] Only recently has this reaction been claimed to be of general applicability.[9] Consideration of the mechanism operative during the above transformations suggests a reaction course similar to that of the Arbuzov reaction.[10]

Heterocyclic N-oxides are known to be capable of electrophilic attack on oxygen.[11] In view of this interesting chemical property of these N-oxides and because such nucleophilic reactivity is encompassed in the first step of the general mechanism under consideration, it was of interest to determine if suitable 2-alkoxy heterocyclic N-oxides would enter into a related reaction. The present report describes our results on the reaction of 2-ethoxypyridine-1-oxide (I) and 2-ethoxyquinoline-1-oxide (II) with various primary and secondary halides.

DISCUSSION AND RESULTS

Strong support for the contention that the N-oxide reaction would proceed along a similar path was found in the existing literature; treatment of I and II with aqueous

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[1] Part XV: L. A. Paquette, *Tetrahedron Letters*, 1291 (1965).

[2] Fellow of the Alfred P. Sloan Foundation.

[3] Present address: Department of Chemistry, The Ohio State University, Columbus 10, Ohio, U.S.A.

[4] L. Knorr and P. Rabe, *Ber. Dtsch. Chem. Ges.* **30**, 927 (1892).

[5] E. Späth and G. Koller, *Ber. Dtsch. Chem. Ges.* **56**, 2454 (1923).

[6] E. C. Taylor, Jr., A. J. Crovetti and H. M. Loux, *J. Amer. Chem. Soc.* **77**, 5445 (1955); E. C. Taylor, Jr. and A. J. Crovetti, *Ibid.* **78**, 214 (1956).

[7] L. A. Paquette and G. Slomp, *J. Amer. Chem. Soc.* **85**, 765 (1963).

[8] It is noteworthy that R. R. Renshaw and R. C. Conn [*J. Amer. Chem. Soc.* **59**, 297 (1937)] report that "2-pyridylbenzylether did not yield a methiodide." Unfortunately the product of this reaction was not characterized.

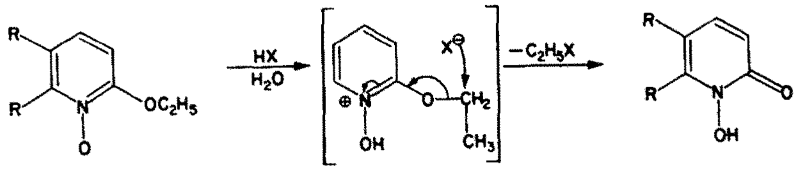
[9] L. A. Paquette and N. A. Nelson, *J. Org. Chem.* **27**, 1085 (1962).

[10] For the latest data on the Arbuzov reaction and leading Refs. to earlier work, *cf.* F. C. Buck and J. T. Yoke, III, *J. Org. Chem.* **27**, 3675 (1962).

[11] *cf.*, *inter alia*, A. R. Katritzky, *J. Chem. Soc.* 2404 (1956); V. Boekelheide *et al.*, *J. Amer. Chem. Soc.* **76**, 1286 (1954); **80**, 2217 (1958); *J. Org. Chem.* **22**, 1135 (1957); W. E. Feely and E. M. Beavers, *J. Amer. Chem. Soc.* **81**, 4004 (1959); J. F. Vozza, *J. Org. Chem.* **27**, 3856 (1962), and pertinent Refs. cited in these papers.

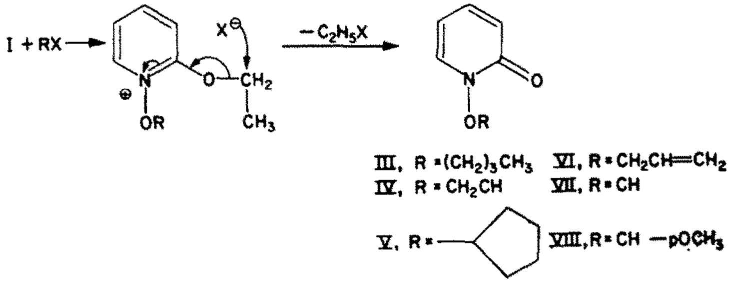
hydrohalogen acids results in the ready formation of N-hydroxy-2(1H)-pyridone and N-hydroxycarbostyril, respectively.[12–14]

The latter reactions can be explained on the basis of the formation of a protonated species which is capable of rapid conversion to the observed products *via* nucleophilic attack at the alkoxy group by halide ion:



I, R = H
II, R = benzo · H_2O

When a mixture of 2-ethoxypyridine-N-oxide (I) and 1-bromobutane was refluxed for 16 hr and the resulting reaction mixture fractionally distilled, there was obtained an 88% yield of 1-(butoxy)-2(1H)-pyridone (III). Structural assignment of the product as III was based on elemental analyses, IR carbonyl absorption at 1665 cm^{-1}, and UV absorption maxima characteristic of the 2(1H)-pyridone system at 227 and 300 mμ.



III, R = $(CH_2)_3CH_3$
IV, R = CH_2CH
V, R =
VI, R = $CH_2CH{=}CH_2$
VII, R = CH
VIII, R = CH —pOCH_3

Ultimate structural confirmation of the cyclic hydroxamic acid esters produced by this procedure was obtained when I was heated with benzyl chloride to give a 92% yield of 1-(benzyloxy)-2(1H)-pyridone (VII), identical in all respects with a sample prepared by a previously described unequivocal route.[15–16]

Treatment of I with allyl bromide likewise produced a high yield of 1-(allyloxy)-2(1H)-pyridone (VI). Secondary halides, exemplified by cyclopentyl chloride, gave reduced yields of products while tertiary halides underwent customary E_2 elimination.

2-Ethoxyquinoline-N-oxide monohydrate (II) was found to undergo similar reactions although in somewhat lower yield.[17] (Table 1)

In summary, the reaction I and II with primary and secondary halides has been

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[12] G. T. Newbold and F. S. Spring, *J. Chem. Soc.* 1864 (1948).

[13] K. G. Cunningham, G. T. Newbold, F. S. Spring and J. Stark, *J. Chem. Soc.* 2091 (1949).

[14] M. Hamana and M. Yamazaki, *Chem. Pharm. Bull. Japan* **10**, 51 (1962).

[15] E. Shaw, *J. Amer. Chem. Soc.* **71**, 67 (1949).

[16] J. N. Gardner and A. R. Katritzky, *J. Chem. Soc.* 4375 (1957).

[17] The lower yields of carbostyrils may be partially due to the difficulty in oxidizing 2-ethoxyquinoline (Ref. 14) and to the subsequent problem of rigidly purifying the N-oxide monohydrate (II).

TABLE 1. SUMMARY OF REACTION CONDITIONS AND ANALYSES

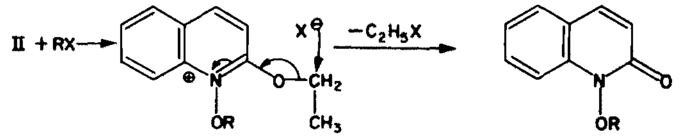
Compd. No.	Reaction Temp, °C.	Hr.	Yield, %	B.p. or M.p., °C.	Formula	Anal. {Calc. Found C	H	N
III	100	16	88·1	97 (0·1 mm)	$C_9H_{13}NO_2$	64·65 64·79	7·84 7·93	8·38 8·37
IV	125–130	16	51·2	165 (0·25 mm)	$C_{13}H_{13}NO_2$	72·54 72·40	6·09 5·82	6·51 6·33
V	120–130	6	37·1	66–67[c]	$C_{10}H_{13}NO_2$	67·02 66·89	7·31 7·29	7·82 7·56
VI[a]	70	3·5	97·3	91 (0·1 mm)	$C_8H_9NO_2$	63·56 63·85	6·00 6·46	9·27 8·91
VII	120	3	92·0	77–78[b]				
VIII	125	1	93·2	76–76·5[c]	$C_{13}H_{13}NO_3$	67·52 67·83	5·67 5·69	6·06 6·33
IX	70	24	69·8	120–121 (0·4 mm)	$C_{12}H_{13}NO_2$	70·91 70·85	6·45 6·21	6·89 6·81
X	70	3·5	61·2	140 (0·3 mm)	$C_{12}N_{11}NO_2$	71·62 71·34	5·51 5·55	6·96 7·02
XI	110–130	2	55·0	104–104·5[c,d]	$C_{16}H_{13}NO_2$	76·47 76·15	5·22 5·30	5·57 5·79

[a] Since the completion of this work, VI has also been prepared by F. J. Dinan and H. Tieckelmann [*J. Org. Chem.* **29**, 1650 (1964)]: 1660 cm^{-1}; $\lambda_{max}^{H_2O}$ 226 (5,500) and 296 mμ (5,400).

[b] Lit.[16] m.p. 76–78°.

[c] Recrystallized from ethyl acetate–hexane.

[d] Recrystallized from ether.



IX, R = $CH_2CH_2CH_3$
X, R = $CH_2CH{=}CH_2$
XI, R = CH

found to be a general one-step synthesis of cyclic hydroxamic acid esters as exemplified by compounds III–XI.

*Studies with 4-ethoxypyridine-*N*-oxide.* Because of the similarity of chemical properties of II and its 4-isomer,[18] it appeared worthwhile to investigate the possibility of employing commercially available 4-ethoxypyridine-N-oxide (XII) as a convenient source of 1-alkoxy-4-pyridones. This result would necessitate that the mechanism outlined above be also operative in the case of XII. As a test of this possibility, a mixture of XII and anisyl chloride was heated at 120° for 3 hr and the mixture directly chromatographed. The ether eluate was distilled to give a good yield of anisaldehyde,

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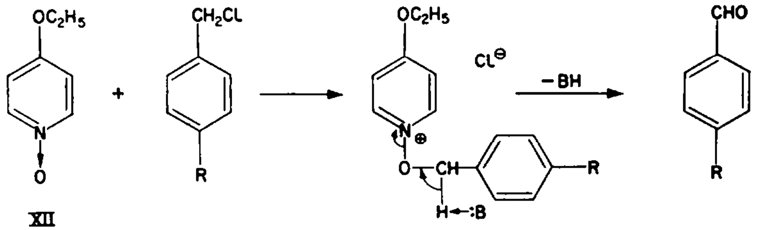
[18] For a helpful review on the general topic of aromatic heterocyclic N-oxides see A. R. Katritzky, *Quat. Revs.* **10**, 395 (1956).

identical in all respects with an authentic sample. In a similar study, benzyl chloride afforded benzaldehyde.[19]


XII

The aldehydes undoubtedly arise from the quaternary salts of the N-oxides which subsequently undergo cleavage to the carbonyl component and 4-ethoxypyridine as shown in the equation. Although the deoxygenation of pyridine-N-oxides by the general procedure of decomposing N-alkoxypyridinium salts with alkali hydroxides is well documented in the literature,[11] these results were somewhat surprising, but suggestive that weaker bases (such as the N-oxide itself) are also capable of promoting the elimination of the heterocyclic moiety.

Numerous reasons for the divergence in reaction pathways for the 2- and 4-ethoxypyridine-N-oxides can be envisioned, but in the absence of more detailed information, enumeration of these would be pointless.

TABLE 2. SPECTRAL COMPARISONS OF THE CYCLIC HYDROXAMIC ACID ESTERS

Compd. No.	Infra-red (cm^{-1})	Ultra-violet (λ_{max} $m\mu$ in 95% EtOH)
III	1665[a]	227 (6,400) and 300 (5,600).
IV	1664[a]	227 (6,000) and 300 (5,550).
V	1660[b]	229 (6,050) and 302 (5,450).
VI	1660[a]	229 (6,000) and 301 (5,400).
VIII	1665[b]	229 (17,600), 275 sh (3,650), 281 (4,450) and 301 (5,900).
IX	1665[a]	230 (39,450), 246 sh (8,400), 271 (6,650), 277 sh (6,100), 316 sh (4,450), 328 (5,550) and 342 sh (3,950).
X	1663[a]	229 (38,250), 245 sh (7,650), 271 (6,800), 277 sh (6,100), 316 sh (4,650), 327 (5,600), and 342 sh (3,850).
XI	1662[b]	230 (37,800), 245 sh (8,150), 271 (6,750), 278 (6,150), 316 sh (4,500), 328 (5,550) and 342 sh (3,800).

[a] Determined as a liquid film.
[b] Determined as a Nujol mull.

EXPERIMENTAL

M.ps are corrected while b.ps are uncorrected. The author is indebted to the Physical and Analytical Chemistry Department of The Upjohn Company for the elemental and spectral analyses.

General procedure. An equimolar mixture of the N-oxide and halide (if the halide was reasonably low boiling, twice the theoretical quantity was employed) was heated at an elevated temp for varying periods of time (Table 1). In the case of the liquid products, the reaction mixtures were directly distilled and the yields are based upon the product obtained over a small b.p. range at this stage. For

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[19] No attempts were made during the workup of these reactions to isolate the pyridine components (presumably 4-ethoxy-pyridine, or its hydrogen chloride hydrolysis product).

solid products, the reaction mixture was cooled, triturated with the appropriate solvent (Table 1), filtered and dried. Recrystallization from the indicated solvents was then effected.

*Reaction of 4-ethoxypyridine-*N*-oxide* (XII) *with anisyl chloride.* A mixture of 7·0 g (0·05 mole) XII and 7·8 g anisyl chloride was heated at 130° for 2 hr with stirring. The resulting brown gum was chromatographed on Florisil[20] and elution with ether gave a fluid pale yellow liquid. Distillation of this material afforded 2·1 g[21] of colourless liquid, b.p. 118° (12 mm), n_D^{21} 1·5630, pure liquid 1690 cm^{-1}. The IR spectra of this material and that of an authentic sample of anisaldehyde were superimposable.

Reaction of XII *with benzyl chloride.* A mixture of 7·0 g (0·05 mole) XII and 6·4 g (0·05 mole) benzyl chloride was heated at 130° with stirring for 2 hr. A workup similar to that above gave 1·8 g of colourless liquid, b.p. 61° (12 mm), identical in all respects with a known sample of benzaldehyde.

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[20] Florisil is a magnesia–silica gel adsorbent manufactured by the Floridin Company.

[21] The yield of this and the subsequent reaction are definitely not optimal.