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N-OXIDES AND RELATED COMPOUNDS—XXXV*

REACTIONS OF N-ALKOXY-PYRIDINIUM AND -QUINOLINIUM CATIONS WITH NUCLEOPHILES

A. R. KATRITZKY and E. LUNT

School of Chemical Sciences, University of East Anglia, Norwich

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Abstract—Numerous new examples of reactions of N-alkoxy and N-acyloxy heterocycles with nucleophiles are classified into four types. The dependence of the reaction path on the hard/soft nature and other characteristics of the nucleophiles is discussed, and a rationalisation provided for the varied products produced under different conditions.

PREVIOUSLY[1] the reactions of 1-alkoxypyridinium salts with nucleophiles were found to occur by four distinct pathways (Paths A–D, Scheme 1). The present paper extends this classification to other reactions of alkoxypyridinium salts, particularly with soft[2] and very soft nucleophiles, and to the reactions of N-alkoxy-quinolinium and -isoquinolinium salts. Most such reactions with 1-methoxypyridinium salts cause demethylation (reaction type C), but type D reaction occurs with piperidine and type B reaction with borohydride ions. A similar pattern with minor deviations (see below) applies to quinolinium and isoquinolinium salts.

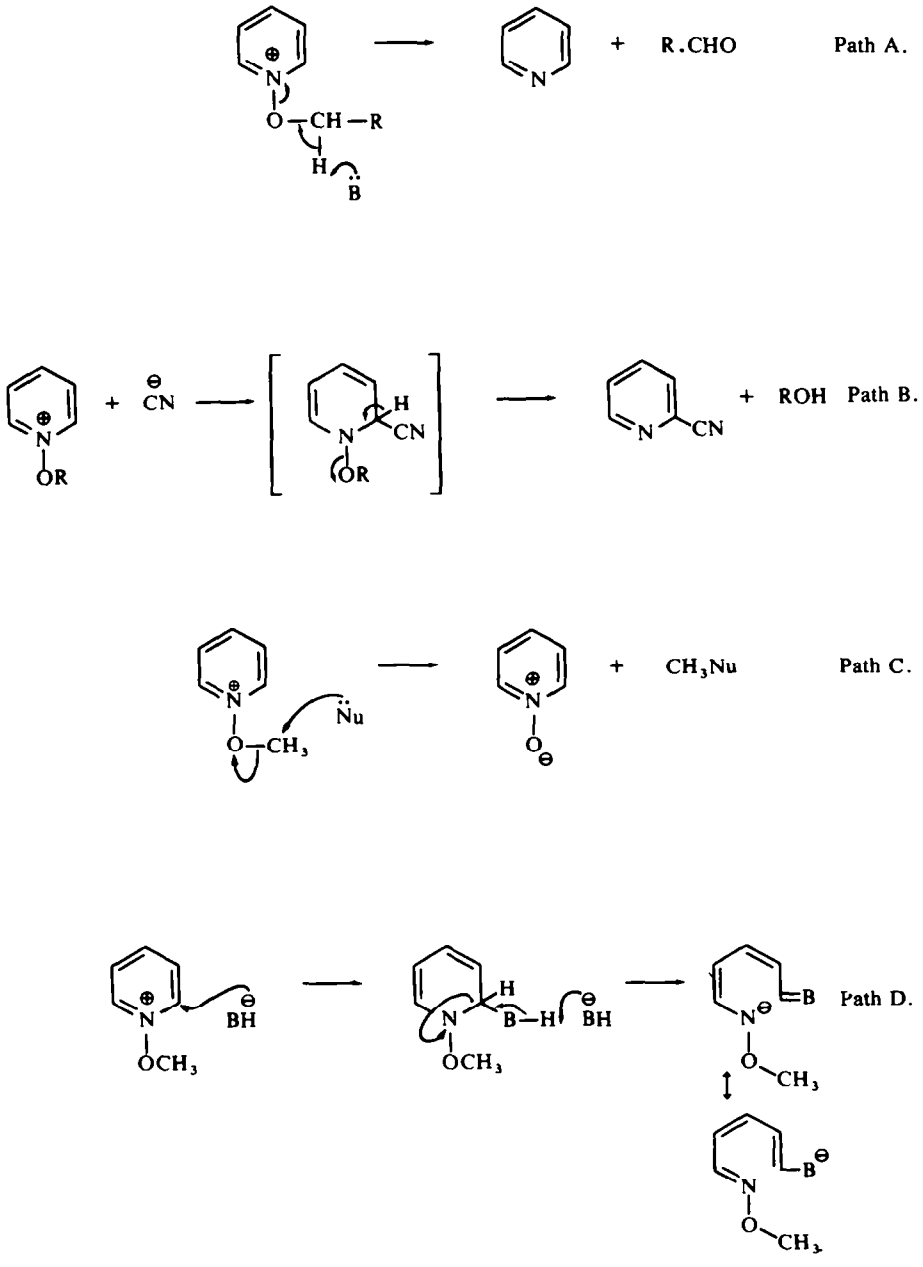
Preparation of substrates. N-Methoxy-pyridinium, -quinolinium and -isoquinolinium salts were prepared from the corresponding N-oxides with methyl toluene-*p*-sulphonate or dimethyl sulphate by known methods.[3,4] 1-t-Butoxypyridinium perchlorate (I), obtained by reaction of the N-oxide with t-butyl bromide and silver perchlorate in nitromethane, slowly solvolysed in aqueous solution to pyridine 1-oxide and t-butanol as shown by the NMR spectrum (Fig. 1). The first-order solvolytic rate constant was independent of hydroxide ion concentration {k_1 (min^{-1}) = 1·56 ± 0·02 at 25° for [OH^-] varying from zero to 2·5 × 10^{-3}N; at higher [OH^-] ring opening by path D competes} indicating an S_N1 mechanism. The perchlorate decomposed on heating in polar aprotic solvents to the N-oxide and t-butylene; this E1 process could also be followed in the NMR spectrum.

1-Phenoxypyridinium salts would be useful for the kinetic studies of type B and/or D reactions as they cannot undergo reactions of types A and C. Phenylations of pyridine 1-oxide with diphenyl iodonium bromide[5] or benzene diazonium fluoroborate failed, as did initial attempts to react phenoxyamine with pyrylium salts (cf. Ref. 6). Incidentally we developed a practical new synthesis of pyrylium perchlorate (II → IV).

Reactions of N-*methoxy salts with nucleophiles.* With nitrite, iodide, thiosulphate, azide, thiocyanate and benzenesulphinate anions, 1-methoxypyridinium salts undergo type C reactions yielding pyridine 1-oxide; sometimes the methylated nucleophile was

* Part XXXIV, Altaf-ur-Rahman, A. J. Boulton, D. P. Clifford, and G. J. T. Tiddy, *J. Chem. Soc.* (B), 1516 (1968).

SCHEME 1



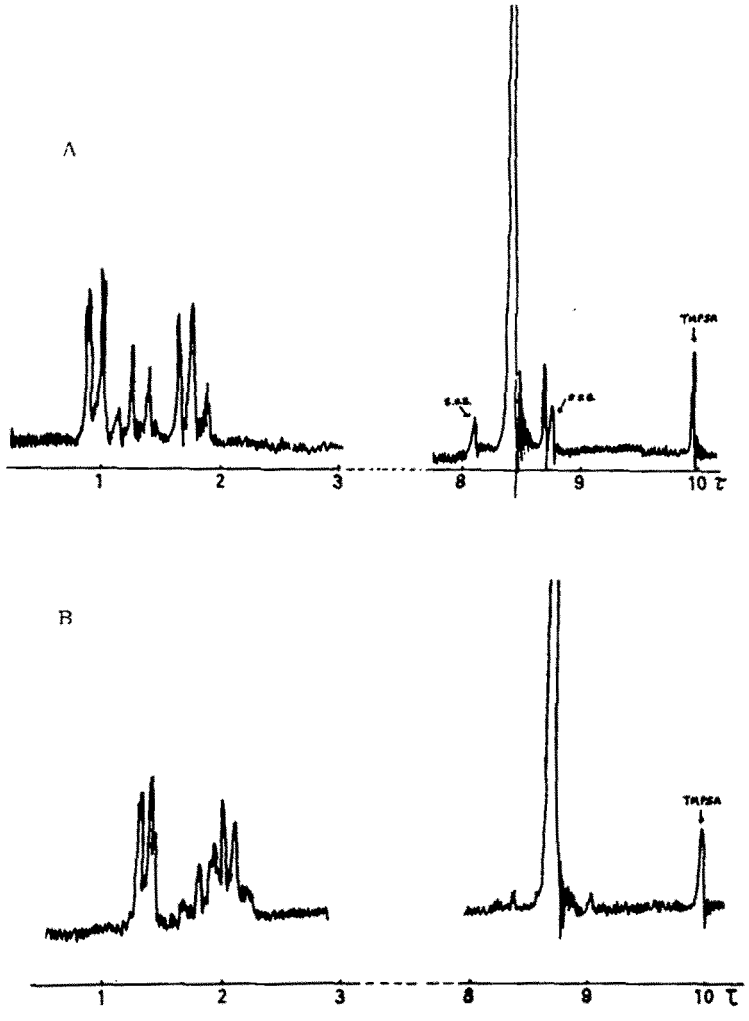
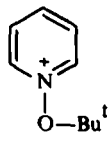


FIG. 1 NMR spectra at 60 Mc/s of 1-t-butoxypyridinium perchlorate in water: (A) after 30 min at room temperature, (B) after 2 hr at 95°.



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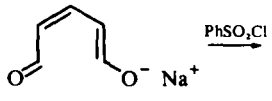

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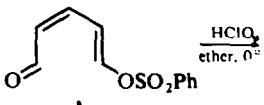

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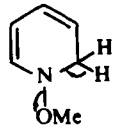

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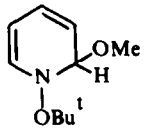

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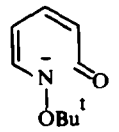


VII

also isolated (Table 1). Piperidine caused type D ring-opening as expected;[1] the unstable products (*cis–trans* and *trans–trans* isomers?) could not be isolated pure, but UV and NMR spectra were observed for typical glutaconic derivatives. Borohydride anion gave, apparently *via* irreversible formation of the dihydro derivative (V), either pyridine, or when present in excess, products of further reduction. Attempts to trap the intermediate (V) by reaction with electrophiles, e.g. acetic anhydride, proved unsuccessful.

Reactions with N-methoxy-quinolinium and -isoquinolinium salts generally resembled those for the pyridinium analogues (Table 1). An exception was that no type D ring-opening reaction was observed with piperidine; this is attributed to interference with the resonance stabilisation of the glutaconic anion due to the presence of the aromatic ring system (cf. Ref. 7). The quinoline formed in some reactions with sulphur nucleophiles may arise from the reduction of initially formed N-oxide (cf. Ref. 8, 9) rather than by path A reaction.

1-*t-Butoxypyridinium perchlorate*. Attempted reactions of this salt with nucleophiles in aqueous solution usually resulted only in the S_N1 decomposition. Generally no reaction was observed at room temperature in aprotic solvents and on heating only pyridine 1-oxide was obtained. Presumably this was formed by E1 decomposition; no t-butylated nucleophile products were detected.

Admixture with methanolic methoxide ion gave NMR spectra (Fig. 2) consistent with the expected type B intermediate (VI), but only polymer was isolated. Similar polymers resulted from attempts to promote type B substitutions using base catalysis with potassium t-butoxide. These reactions are being further investigated.

TABLE 1. REACTION OF N-METHOXY PERCHLORATES WITH NUCLEOPHILES

Series	Nucleophile	Solvent[a]	Temp (deg)	Time (hr)	Products[b]	N-oxide picrate, m.p. (deg)	N-Methyl nucleophile m.p. (deg)
Pyridinium	NO_2^-	DMF	25	24	N-oxide	182°	—
	I^-	EtOH –acetone	25	6	N-oxide	—	—
	$S_2O_3^=$	H_2O	80	12	Complex mixture	—	—
	N_3^-	H_2O	85	9	N-oxide	180–181	—
	NCS^-	EtOH–acetone	25	1·5	N-oxide	—	—
	$PhSO_2^-$	H_2O	100	24	N-oxide	181–182	87
	$PhSO_2^-$	DMF	25	120	N-oxide	180–181	85–87
	piperidine	None	25	24	Glutaconic anions	—	—
	BH_4^-	Borate buffer pH 8·0	25	1	pyridine	162–163[c]	—
Quinolinium	NO_2^-	DMF	25	72	N-oxide	136–137	—
	NO_2^-	H_2O	25	48	N-oxide + quinoline	—	—
	NO_2^-	H_2O	100	18	N-oxide + quinoline	—	—
	NCS^-	DMF	25	60	N-oxide + quinoline	—	—
	NCS^-	H_2O	100	20	N-oxide + quinoline (trace)	140–141	—
	N_3^-	H_2O	25	150	*d*	—	—
	N_3^-	H_2O	80–85	9	N-oxide	139–140	—
	$PhSO_2^-$	H_2O	25	72	*d*	—	—
	$PhSO_2^-$	H_2O	100	6	N-oxide	138–139	86–87
	$PhSO_2^-$	DMF	25	192	N-oxide	140–141	86–87
Isoquinolinium	piperidine	H_2O	95	1	N-oxide +isoquinoline	—	—
	$PhSO_2^-$	H_2O	25	18	*d*	—	—
	$PhSO_2^-$	H_2O	100	11	N-oxide	166–167	—

[a] DMF = dimethylformamide.
[b] Products were detected by UV and/or TLC.
[c] Pyridine picrate.
[d] No reaction.

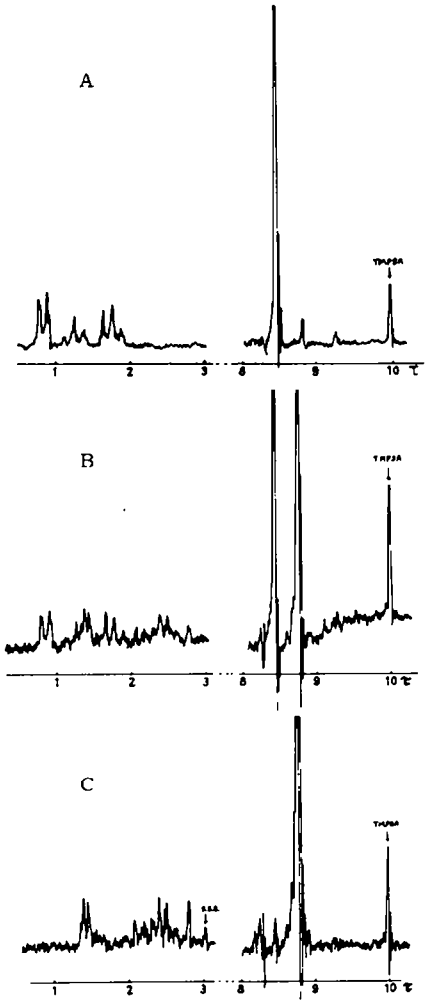


FIG. 2 NMR spectra at 60 Mc/s of 1-t-butoxypyridinium perchlorate in methanol: (A) alone, (B) in 0·3 N-NaOMe, (C) in 0·6 N-NaOMe.

Aqueous hydroxide ion (> 0·1N) led to the type D reaction previously observed[1] with the corresponding N-methoxy salt. The competing S_N1 solvolysis is independent of alkali strength, and is relatively unimportant at the higher hydroxide concentrations (0·4–1·4N) for which type D kinetics were followed, as for the N-methoxy compound, by the increase of the ultraviolet peak at 341 mμ, attributable to the ion (VII) (cf. Ref. 1). Initial rates were obtained (as previously) by plotting O.D. (341 mμ) against time for the first portion of the reaction. If path D is followed and the side reactions can be neglected, Eq. (1), as obtained[1] in the

$$\text{Initial rate} = k_{obs}\,[Py^+]\,[OH^-]^2 \qquad (1)$$

previous work on the 1-methoxy compound, should hold.

Plotting log (initial rate) against log $[OH^-]$ (for constant substrate concentration),

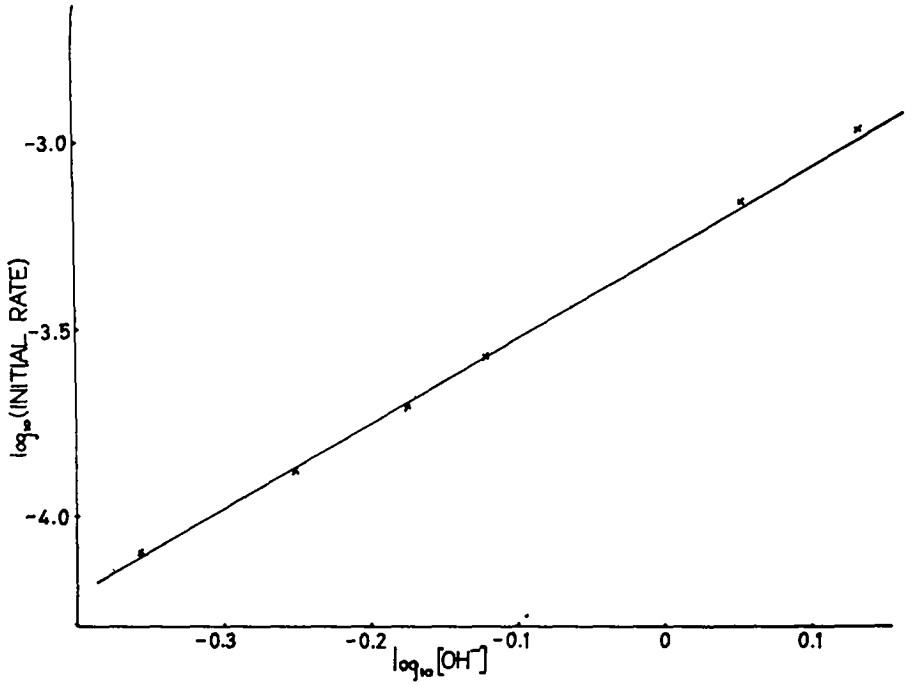


FIG. 3 Plot of log (initial rate) versus log [OH^-] for reaction of 1-t-butoxypyridinium perchlorate with hydroxide ion.

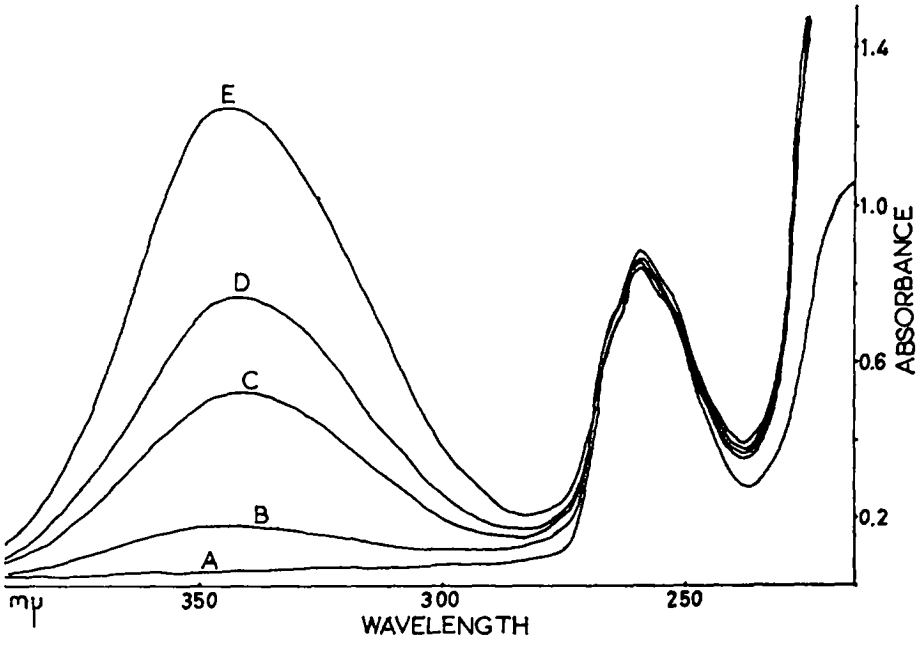


FIG. 4 UV spectra of 1-t-butoxypyridinium perchlorate (A) after addition of 2 vols water, (B) 2 min after addition of 2 vols of 1·77 N KOH, (C) as B after 7 min, (D) as B after 10 min, (E) as B after 15·5 min.

gave a slope of 2·3 (Fig. 3) which is in reasonably good agreement (with the expected 2·0) in view of the concurrence of at least two side reactions. The occurrence of these side and reversible reactions[1] over prolonged reaction time was amply demonstrated by the falling off of the absorption at 341 mμ (Fig. 4), and by the observation of at least five tertiary butyl resonances in the strongly time-dependent NMR spectrum (Fig. 5), one of which was shown to be from t-butanol.

The k_{obs} value obtained from the intercept of the initial rate plot was 3·25. The difference from the value of 23·7 found[1] for the N-methoxy compound seems reasonable in view of the steric and electronic differences involved.

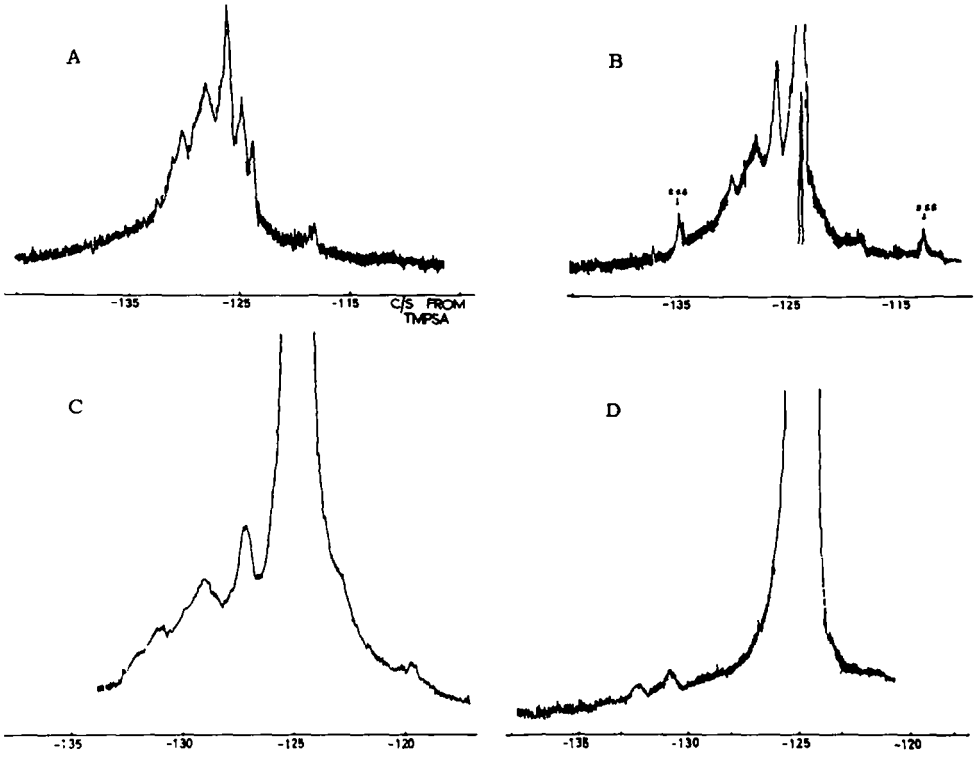
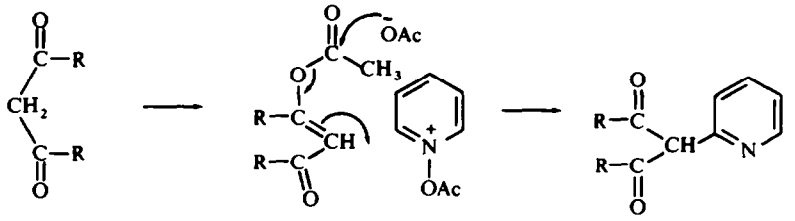


FIG. 5 Expansion of τ 8·8 resonances (100 Mc/s) from reaction of 1-t-butoxypyridinium perchlorate with excess KOH in aqueous methanol: after (A) 6 hr, (B) 7½ hr, (C) 5 days and (D) 40 days.

N-*Acyloxy and -arylsulphonoxy quaternary salts.* These derivatives, prepared *in situ* by reaction of the N-oxide with, e.g. acetic anhydride or benzenesulphonyl chloride, give type B substitution products with nucleophiles such as enamines,[10] indoles,[11,12] pyrroles,[11] antipyrine[11,13] and dialkylanilines.[14] In bicyclic compounds, the lower loss of resonance energy allows formation of the dihydro intermediate (cf. Ref. 15).

Hamana[16] postulated that the reaction of active methylene compounds with N-oxides in the presence of acetic anhydride involved attack by the stabilized carbanion on the N-acetoxy cation. Alternative mechanisms (cf. VIII → IX) involving an enol acetate intermediate are now excluded by the formation of the expected derivative with malonodinitrile. Failure of benzyl cyanide to react[16] is probably due to the low acidity

of the methylene protons ($pK_a > 16$), in agreement with our failure to induce reaction with phenylacetylene (pK_a *ca.* 20).



VIII IX

TABLE 2. REACTION PATHS FOR SOME NUCLEOPHILES WITH N-METHOXYPYRIDINIUM SALTS

	Nucleophile	Solvent	Path	Ref.
soft ↑	$S_2O_3^=$	water	C	[a]
	$SAlk^-$	alkanethiol, ethanol	A + B + C	9, 43
	SPh^-	ethanol	B + C(+A?)	9
	SO_2Ph^-	water, dimethylformamide	C	[b]
	SCN^-	methanol, ethanol-acetone	C	[a]
	I^-	ethonol-acetone	C	[a]
	CN^-	water, various buffers	B	4, 19, 24
	AlkMgBr	ether	B	26
	ArMgBr	ether	C?	43
	N_3^-	water	C	[b]
	NO_2^-	water, dimethylformamide	C	[b]
	piperidine	none	D	[b]
	morpholine	none	C	43
	$ArNH_2$, ArNHMe	none	C	43
	OAc^-	acetic acid	C	43
hard ↓	BH_4^-	water, borate buffer (pH 8)	B	[b]
	OMe^-	methanol	A	43
	OPh^-	ethanol	A	43
	OH^-	water	A+D	1

[a] R. Eisenthal, personal communication.
[b] This work.

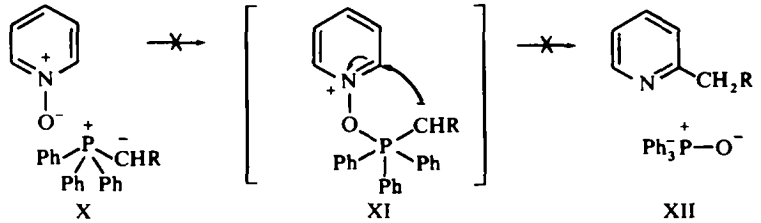
DISCUSSION OF RESULTS

The modes of reaction of the 1-methoxypyridinium ion with nucleophiles (summarized in Table 2) are clearly influenced by several factors. (i) The structural nature of the nucleophile; thus, ring-opening by path D requires an acidic hydrogen attached to the nucleophilic centre. (ii) The "hardness" and "softness" of the nucleophile as defined empirically by Pearson,[2] or more rigorously by the MO method of Hudson and Klopman,[17] differentiates between path A attack at a hard hydrogen centre, and paths B or C involving attack at relatively soft carbon centres. This expectation is broadly borne out by the results as shown in Table 2. A subsidiary effect of hardness/softness is the ability of the nucleophile to remove the 2-proton from the dihydro intermediate of path B, a process which will also be affected by the

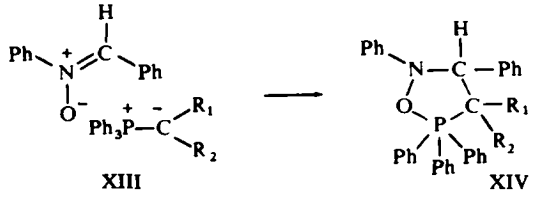
electron-withdrawing or -donating properties of the substituted nucleophilic group. (iii) Differentiation between attack at the 2- or 4-position is determined by subtle questions of kinetic *vs* thermodynamic control [18] and other steric and mechanistic factors, and less by hardness/softness considerations (cf. Ref. 16). (iv) Direct steric effects in the substrate, minimized in the N-methoxy series, are important with the t-butoxy compound and with longer alkyl chains.[19] Steric effects in the S_NAr transition state may also be important.[20]

For nuclear attack by paths B or D, the initial step leading to the dihydropyridine intermediate is reversible whenever the entering nucleophile is also a good leaving group. Such equilibria favour reactants as the dihydro intermediates have not been detected in our UV or NMR studies (Meisenheimer complexes in the pyridine series were detected[21] only for polynitro derivatives). Our kinetic results on the reactions of the N-methoxy and N-t-butoxy salts with hydroxide ion, together with previous results[22] on the reaction of amines with 2,4-dinitrophenylpyridinium ions, are in agreement.

The strength of the nucleophile determines the ability of the nucleophile to initiate ring attack, which involves a considerable loss of resonance energy, particularly in the monocyclic systems. Thus weak nucleophiles are either unable to initiate the first step in path B, or the equilibrium lies too far towards reactants. The importance of this factor is illustrated by the increased importance of path B in the bicyclic systems, and by our failure to achieve a path B type cyclization reaction (X → XII) of pyridine 1-oxide with the Wittig reagent,* the open-chain analogue of which (XIII → XIV), and also the analogous reaction with 3,4-dihydroisoquinoline 2-oxide, have recently been reported by Huisgen.[23] The effects of loss of resonance energy in S_NAr reactions in the dinitronaphthalene series have been discussed from a similar viewpoint.[15]



X XI XII



XIII XIV

* Professor Hamana in a personal communication informed us that this reaction also failed in the quinoline series.

Certain quite strong nucleophiles such as iodide and azide anions, which might be expected to give B-type ring substitution, react by path C; presumably the initial reversible equilibrium is established but the rate-determining loss of proton from the dihydro intermediate is too difficult in the absence of a strongly activating effect, or of a strongly basic species, to assist in proton removal.

It is now clear why successful path B reactions have been observed with only four types of nucleophile, *viz*: cyanide,[4,24] mercaptide,[9,25] and borohydride ions, and certain carbanions from Grignard reagents[26] or active methylene compounds.[27] For borohydride ion and the carbanions, the first step of the reaction is essentially irreversible. For cyanide and mercaptide ions, although the first step is reversible, the electron-withdrawing nature of the substituent group coupled with the pronounced basic nature of both nucleophiles[17] assists the tate-determining deprotonation stage, Cyanide ions should also be free from steric effects in the S_NAr transition state. although this is not regarded as a primary determining factor.

These generalizations are intended to serve as a basis for further research in both the synthetic and kinetic-mechanistic fields, by which the conclusions presented may be tested.

EXPERIMENTAL

Materials. Compounds were prepared by the methods indicated: pyridine 1-oxide,[28] (92%) b.p. 137–141°/12 mm, m.p. 66–67° (from EtOAc); picrate,[29] m.p. 181–182°; quinoline 1-oxide,[4] (68%) b.p. 147–152°/0·6 mm, m.p. 51–52° (from diisopropylether), picrate,[29] m.p. 139–140°; isoquinoline 2-oxide,[30] (82%) b.p. 170 /3 mm, m.p. 99–101° (from diisopropyl ether), picrate,[30] m.p. 165–166°; methyl phenyl sulphone,[31] m.p. 87° (from diisopropyl ether).

1-Methoxypyridinium perchlorate[1] had m.p. 68–69° (from absolute EtOH); NMR: (D_2O) τ 0·78 (2H, m) 1·31 (1H, m) and 1·77 (2H, m) (aromatic), and 5·46 (3H, s) (OMe); (CF_3COOH) τ 1·17, 1·52, 1·93 and 5·54.

1-Methoxyquinolinium perchlorate

(a) Quinoline 1-oxide (19·8 g) and methyl toluene-*p*-sulphonate (25·4 g) were heated at 120° for 8 hr. Dissolution in hot water (50 ml), decolorization (C) and treatment with solid $NaClO_4$ (50 g) gave, on cooling to 0°, the perchlorate (15·6 g, 44%), m.p. 111–112° (lit.[32] m.p. 112°) (Found: C, 46·0; H, 4·1; N, 5·0. Calc. for $C_{10}H_{10}ClNO_5$: C, 46·2; H, 3·6; N, 5·4%). *Picrate*, m.p. 155–156° (Found: C, 50·0; H, 3·4; N, 14·6. $C_{16}H_{12}N_4O_8$ requires: C, 49·5; H, 3·1; N, 14·5%). Alternatively, the melt from the N-oxide (18·6 g) and the ester (23·9 g) was dissolved in hot dry EtOH (80 ml), 70% $HClO_4$ (30 ml) added, and the mixture diluted with EtOAc (200 ml) to give the crude perchlorate, m.p. 107–110° (20·7 g, 70%), crystallized from MeOH (16·9 g, 57%), m.p. 110–111°.

(b) The N-oxide (19·5 g) and Me_2SO_4 (12·8 ml) were mixed, and when the initial reaction had subsided, heated at 95° for 2 hr, cooled, and the melt dissolved in dry EtOH (25 ml). 70% $HClO_4$ (14 ml) was added and the product precipitated with EtOAc (100 ml) to give, after crystallization from MeOH, the perchlorate (22·7 g, 65%), m.p. 110–111°. UV: 237, 315 mμ (log ε 4·51, 3·81) NMR: (D_2O) τ 0·35 (H_2), 0·78 (H_4), 5·37 (OMe); (CF_3COOH) τ 0·71 (H_2), 0·97 (H_4), 5·42 (OMe).

Isoquinoline 2-oxide (20·8 g) and methyl toluene-*p*-sulphonate (26·7 g), gave *2-methoxyisoquinolinium toluene-p-sulphonate* (26·8 g, 57%) as above, the cooled melt being twice crystallized from EtOH/EtOAc, m.p. 139–140° (depends on heating rate) Found: C, 62·4; H, 5·4; N, 4·0. $C_{17}H_{17}NO_4S$ requires: C, 61·6; H, 5·2; N, 4·2%). *Picrate*, m.p. 154–155° (Found: C, 49·8; H, 3·4; N, 14·6. $C_{16}H_{12}N_4O_8$ requires: C, 49·5; H, 3·1; N, 14·5%).

2-Methoxyisoquinolinium perchlorate

The N-oxide (18·3 g) and Me_2SO_4 (15·9 g) were mixed, allowed to react, then heated at 95° for 2 hr. The cooled melt was dissolved in dry EtOH (20 ml), 70% $HClO_4$ (13 ml) added and the perchlorate, m.p. 94–99° (19·6 g, 60%) precipitated with EtOAc (150 ml). Crystallization from MeOH gave material m.p. 101–102° (lit.[33] m.p. 104°). NMR: (CF_3COOH) τ 0·36 (H_1), 5·47 (OMe).

1-(t-Butoxy)pyridinium perchlorate

To dry pyridine 1-oxide (9·5 g, 3 mol) and t-butyl bromide (4·6 g) in dry nitromethane (5 ml), was added with stirring over 2½ hr at 0° $AgClO_4$ (7 g) *in dry nitromethane*[34] (20 ml). The mixture was stirred at 0° for 4 hr, then allowed to warm slowly to 20°. AgBr was filtered off and washed with nitromethane. The combined nitromethane solns were washed with water (3 × 100 ml) [pyridine 1-oxide (3·4 g) was recovered from the washings], dried ($MgSO_4$) and diluted with ether to give the crude salt (1·7 g; 20%), m.p. 90–92°. Crystallization from water gave *t-butoxy salt* (1·3 g, 16%), m.p. 95–96° (Found: C, 42·9; H, 5·5; N, 5·4. $C_9H_{14}ClNO_5$ requires: C, 42·9; H, 5·6; N, 5·6%). On a large scale the N-oxide (19 g, 1 mol) with t-butylbromide (27·5 g) and $AgClO_4$ (39·3 g) gave on trituration of the crude salt from the nitromethane/ether with ice-water, the perchlorate (11·2 g, 22%), m.p. 95–96°; UV: 258 mμ (log ε 3·63) NMR: (D_2O), τ 0·98 (2H, m) ($H_{2,6}$), 1·30 (1H, m) (H_4), 1·79 (2H, m) ($H_{3,5}$) and 8·46 (9H, s) (O–t-Bu).

The *picrate* had m.p. 182–183° (from EtOH) (Found: C, 47·1; H, 4·2; N, 14·8. $C_{15}H_{16}N_4O_8$ requires: C, 47·4; H, 4·2; N, 14·8%).

5-(Benzenesulphonyloxy)penta-2,4-dienal

Crude glutaconic aldehyde sodium salt,[35] crystallized (pyridine-water) (85:15) to give yellow plates (45%) UV: 362·5 mμ (log ε 4·73) in 2·8 × 10^{-3} N NaOH [lit.[36] UV: 362·5 mμ (log ε 4·75) in DMF/Et_3N].

The purified sodium salt (0·4 g) and benzenesulphonyl chloride (0·44 g) in water (5 ml) were shaken vigorously with ice-cooling for 1 hr. The mixture was extracted with $CHCl_3$ (4 × 10 ml, freed from EtOH by passage through Al_2O_3) and the extracts dried over $MgSO_4$. The IR spectrum of the extract showed ν_{max} 1680 (C=C) and 970 (C—H *trans*) cm^{-1}.

Evaporation under reduced pressure gave the dienal as an unstable yellow oil (0·46 g, 76%); NMR: ($CDCl_3$) τ 0·45 (1H, d) (H_A), 2·80 (1H, d) (H_E), 2·97 (1H, q) (H_C), 3·82 (1H, q) (H_D), 3·86 (1H, q) (H_B); J_{AB} = 7·6, J_{BC} = 15·1, J_{CD} = 10·9, J_{DE} = 12·6 c/s.

Pyrylium perchlorate

The above dienal (0·32 g) in ether (5 ml) was treated with 70% $HClO_4$ (0·5 ml) in ether (10 ml) at 0°, a little MeOH being added to give a homogeneous soln. After 18 hr at 0° the crystalline perchlorate was filtered off (70 mg, 29%) and washed with ether, m.p. 296–297° (explodes) (lit.[37] explodes 275°). The IR spectrum (Nujol) was identical with that given by Balaban.[38]

Reactions of 1-methoxypyridinium perchlorate

The following procedures are intended to illustrate the results summarised in Table 1. For full details see Ref. 39.

(a) *Sodium borohydride.* To the methoxy salt (0·52 g) in borate buffer[40] (100 ml; pH 8·0) was added with stirring at 25° a soln of $NaBH_4$ (0·05 g) in borate buffer (5 ml). After 48 hr (UV spectrum unchanged), further $NaBH_4$ (0·3 g) was added and the mixture stirred for 1 hr, when the UV spectrum indicated that all the starting material had been reduced. Extraction with ether (2 × 30 ml) and treatment of the extract with ethereal picric acid gave pyridine picrate (0·12 g), m.p. and mixed m.p. 162–163° after crystallization from EtOH.

(b) *Piperidine.* The perchlorate (1 g) and piperidine (10 ml) were kept for 24 hr. The UV spectrum then showed the disappearance of starting material and the appearance of a broad band at 345 mμ, similar to that previously observed[41] in the piperidine-induced ring-opening of a bicyclic alkoxypyridinium salt.

The mixture was evaporated at 35°/10 mm, then kept *in vacuo* over conc H_2SO_4 for several days. The gum was extracted with ether to give an extract which showed the 345 mμ UV absorption. Attempts to prepare stable picrate or diptolate[42] salts from this extract were unsuccessful. Evaporation, however, followed by keeping *in vacuo* over conc H_2SO_4 gave an orange oil whose NMR spectrum (d_6-DMSO) showed in addition to broad peaks corresponding to piperidine-ring protons at τ 8·47, 6·97, two N-OMe singlets at τ 6·27, 6·24 and the characteristic[41] high-field vinyl quartet at τ 4·73 (J = 10·4, 12·6 c/s), together with a complex set of other vinyl peaks in the range τ 2·2–4·5.

The gummy residue from the ether extraction contained piperidine perchlorate and probably some pyridine 1-oxide formed by the concurrent S_N2 reaction, by analogy with the results in the case of morpholine.[43]

(c) *Sodium benzenesulphinate.* The methoxy salt (1 g) and sodium benzenesulphinate dihydrate (1·13 g) in water (20 ml) was refluxed for 3 hr, and allowed to cool overnight. The mixture was diluted with

water, extracted with ether (2 × 20 ml), the ether extracts dried ($MgSO_4$) and evaporated to give crude methyl phenyl sulphone (0·36 g), m.p. 76–78°. Crystallization from diisopropyl ether gave the pure sulphone (0·22 g, 30%), m.p. and mixed m.p. 85–86°.

Continuous extraction of the aqueous liquors with CH_2Cl_2 gave pyridine 1-oxide, isolated as picrate (0·27 g, 18%), m.p. 177–178°, mixed m.p. with authentic sample undepressed.

As no other products were observed on TLC it seemed likely that incomplete reaction had occurred. This was confirmed by the isolation after 24 hr reflux of the sulphone (0·4 g, 54%), m.p. 87° [together with less pure material (0·25 g, 34%), m.p. 80–81°], and pyridine 1-oxide (as picrate) (0·41 g, 53%), m.p. and mixed m.p. 181–182°.

Reactions of 1-*(t-butoxy)pyridinium perchlorate*

(a) S_N1 *Decomposition in water—UV study.* The UV spectra of appropriate dilutions of a stock solution, freshly prepared from the perchlorate (56·8 mg) in water (250 ml), showed a progressive change of the peak due to the salt at 258 mμ (log ε 3·63) to that due to pyridine 1-oxide (255 mμ, log ε 4·0). After complete decomposition, several solutions gave a total of 83 mg perchlorate gave pyridine 1-oxide, as picrate, (48 mg, 52%), m.p. and mixed m.p. 181–182°.

The first order rate constants for the decomposition in water and in $4·5 \times 10^{-4}$ N- and $2·5 \times 10^{-3}$ N-KOH were determined as follows. The t-butoxy salt (1 ml of a solution of 36·0 ± 0·1 mg in 100 ml of water) was diluted to 10 ml with water and thermostatted at 25° ± 0·1. The absorption at 258 mμ was determined at intervals against a water blank. The "infinity" reading was taken after at least 6 half-lives (16–18 days). Log ($OD_\infty - OD_t$) was plotted against time and from the slope the first-order rate constant was obtained by a least squares method. Similarly, first-order rate constants were obtained when the initial salt solution was diluted with $2·8 \times 10^{-3}$ N- and 5×10^{-4} N-KOH solution, and the OD (258 mμ) determined at intervals against the appropriate blank.

(b) S_N1 *Decomposition in water—NMR study.* The t-butoxy salt (54·3 mg) in water (0·6 ml) with 3-(trimethylsilyl)propane sulphonic acid sodium salt (TMPSA) as internal reference, was heated at 95° for 2 hr, when the NMR spectrum (Fig. 1) showed the disappearance of the t-butoxy peak at τ 8·45 and appearance of the t-butanol singlet at τ 8·73, together with the change in the aromatic A_2B_2C salt pattern to that for pyridine 1-oxide, displaced from the usual τ-values due to the presence of $HClO_4$ (cf. Ref. 44).

(c) *Reaction with hydroxide ion—UV study.* A stock soln of the t-butoxy salt (approx. $3·2 \times 10^{-4}$M) was prepared in water and stored at 0°, being equilibrated rapidly to 25° in a constant temp bath just before reaction with the hydroxide. The S_N1 decomposition was sufficiently slow to allow kinetic runs with different hydroxide concentrations. To the stock solution (1 ml, at 25°) in a 1 cm silica UV cell was added a measured volume of the appropriate strength KOH soln, zero time being taken as the time of half-addition of the pipette contents. The cell was stoppered, shaken rapidly, and placed in a Unicam SP 500 UV spectrophotometer thermostatted cell-holder/controller (A. Adkins and Sons Ltd., Leicester) with a thermocouple device suspended in the blank cell.[45] The rise in OD (341 mμ) was followed with time, an appropriate correction being made for the absorbance at 341 mμ of the various concentrations of hydroxide against a water blank.

The absorbances were plotted against time and from the initial straight portions of the graphs, initial rates were obtained (least-squares).

(d) *Reaction with hydroxide ion—NMR study.* As the reaction mixture from the t-butoxy salt and hydroxide ion in aqueous solution gradually became turbid, the NMR observations were carried out in the presence of sufficient MeOH to prevent this. No aromatic or vinyl resonances could be observed no doubt due to rapid exchange with the reagent (cf. Ref. 46). In the t-butyl region, however, a broad peak was observed, which on expansion at 100 Mc/s was shown to consist of five peaks. One of these (that at highest field) was shown to correspond to added t-butanol. The others lying at 1·0, 2·4, 4·2 and 6·4 c/s downfield from t-butanol decreased in intensity relative to the t-butanol peak on standing, finally disappearing altogether in agreement with the setting up of a reversible equilibrium (I ⇌ VII), followed by the slow, irreversible S_N1 decomposition to pyridine 1-oxide and t-butanol.

(e) *Reaction with methoxide ion.* The t-butoxy salt (62·7 mg) in 2N-methanolic NaOMe (0·5 ml), with 3-(trimethylsilyl)propane sulphonic acid sodium salt (TMPSA) as reference, rapidly changed from yellow through orange to brown. The NMR spectrum showed no aromatic resonances after 10 min; the t-butoxy peak was shifted from τ 8·45 to 8·77. After standing, the mixture was poured into ice-water, when a brown polymeric material (22 mg) was precipitated. No pyridine 1-oxide was recovered on continuous extraction of the aqueous liquors. When 0·3N-NaOMe was used, the usual aromatic resonances of the t-

butoxy salt were observed, but in addition, a complex series of resonances in the τ 1–3 region was visible, and there was a partial t-butyl shift from τ 8·45 to 8·77 (Fig. 5).

(f) *Reaction with other nucleophiles*. The t-butoxy salt (0·4 g) and sodium benzene sulphinate dihydrate (0·35 g) in DMF (10 ml) were heated at 90–95° for 5 hr, and kept overnight. The DMF was removed under high vacuum (VPC on the distillate showed only DMF was present), and the residue dissolved in water (10 ml), basified with Na_2CO_3 and extracted with $CHCl_3$, first in portions then continuously for 24 hr, to give a total of 0·19 g of brown oil. TLC examination in several solvent systems showed only one major spot corresponding to pyridine 1-oxide, with only traces of other components. Chromatography on silica gel gave on elution with $CHCl_3$ only traces of non-basic material, followed on elution with MeOH by pyridine 1-oxide, isolated as picrate (0·29 g, 56%), m.p. 178–180°; mixed m.p. with authentic sample undepressed.

Similarly reaction with NaN_3 gave only pyridine 1-oxide picrate (74%), m.p. and mixed m.p. 180–181°, and with KCNS the N-oxide picrate (27%), m.p. and mixed m.p. 180–181°.

Reaction of quinoline, 1-oxide with malonodinitrile in Ac_2O.

Malonodinitrile (0·9 g) was added, with stirring and ice-cooling, to quinoline 1-oxide (1·7 g) in Ac_2O (1·45 g). The red mixture set to a solid mass after 5 min. After 20 min, further Ac_2O (2 ml) was added and the mixture stirred for 5 hr, at 0°, then kept overnight. A mixture of CH_2Cl_2/CCl_4 (1:2, 15 ml) was added, and the precipitated solid (1·58 g) filtered off. The liquors were treated with MeOH to decompose excess Ac_2O and kept overnight, when further solid (0·05 g) was obtained. The solid (0·9 g) was crystallized from AcOH to give yellow needles of *2-quinolylmalononitrile* (0·49 g, 40%), m.p. 306°, raised to 306–307° by further crystallization from the same solvent (Found: C, 74·55; H, 3·6; N, 21·6. $C_{12}H_7N_3$ requires: C, 74·55; H, 3·65; N, 21·8%).

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