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Pyrylium Salts and Hydroxylamine in Acid Medium

Synthesis of Pyridine *N*-Oxides from Pyrylium Salts

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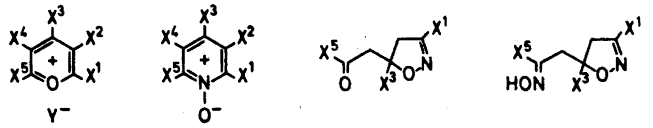
Treatment of highly substituted pyrylium salts with hydroxylamine in acid medium results in the formation of the corresponding pyridine *N*-oxides in good yields. This reaction is compared to the formation of isoxazolinylacetophenones from the same type of pyrylium salts and hydroxylamine under basic conditions. A general mechanism for these reactions, as well as for the closely related reactions of pyrylium salts with phenylhydrazine, is proposed.

The reaction between pyrylium salts and hydroxylamine has previously been the subject of several studies.[1–4] It was reported that treatment of pyrylium salts with hydroxylamine led to the formation of pyridine *N*-oxides, but only when one of the substituents in the 2- or 6-position was not too large. Thus Schmitz [1] obtained 2-methyl-4,6-diphenylpyridine *N*-oxide and 2,4,6-trimethylpyridine *N*-oxide from the parent pyrylium ion and hydroxylamine in ethanol under basic conditions. Balaban and Nenitzescu [2] found that treatment of 2,4,6-trimethyl- and 2,6-diethyl-4-methylpyrylium salts with hydroxylamine in alkaline aqueous medium gave the corresponding pyridine *N*-oxides in decreasing yields. In the latter report it was proposed that the lack of formation of *N*-oxide from the 2,6-diisopropyl-4-methyl- and 2,6-diphenyl-4-methylpyrylium salts was due to steric hindrance.

More recently the reaction between a series of 2,4,6-triarylpyrylium salts (I) and hydroxylamine under basic conditions was examined [3,4] and it was shown that no formation of the corresponding amine *N*-oxides (II) took place. Instead the isoxazolinylacetophenones (III) were formed *via* thermally unstable intermediates (XI – XII A (Chart 3)).

This paper describes the reaction between a series of polyarylpyrylium salts (I) and hydroxylamine in acid medium. It was found that the product distribution is highly dependent on the medium (*i.e.* acidic or basic conditions). There is satisfactory analogy between the dependence of the product distribution on medium found in this study with that of the reaction between pyrylium

salts and phenylhydrazine [3,5–9] to allow some general mechanistic conclusions to be drawn.



I II III(a-c) IV(a-c)

	X^1	X^2	X^3	X^4	X^5	Y^-
a	C_6H_5	H	C_6H_5	H	C_6H_5	BF_4^-
b	C_6H_5	H	4-BrC_6H_4	H	C_6H_5	BF_4^-
c	4-BrC_6H_4	H	C_6H_5	H	4-BrC_6H_4	BF_4^-
d	C_6H_5	CH_3	C_6H_5	H	C_6H_5	ClO_4^-
e	C_6H_5	C_6H_5	C_6H_5	H	C_6H_5	ClO_4^-
f	C_6H_5	C_6H_5	H	C_6H_5	C_6H_5	Br^-
g	C_6H_5	C_6H_5	C_6H_5	C_6H_5	C_6H_5	Br^-
h	CH_3	H	CH_3	H	CH_3	ClO_4^-

Chart 1.

An additional impetus in undertaking this work was the preparative possibilities of the reactions leading to pyridine *N*-oxides. The usual preparation of polyarylpyridine *N*-oxides by peracid oxidation in many cases gives rather poor yields (see Table 1), and another method was desirable. Furthermore, by peracid oxidation of the parent amine the chief impurity generally consists of unreacted starting material which in many cases has been found to be very difficult to separate from the *N*-oxide. In the present method this problem is not important.

RESULTS

Reactions. The reaction of 2,4,6-triarylpyrylium salts (Ia – c) with hydroxylamine in acid medium (acetic acid-sodium acetate buffer) leads to complex mixtures of products. These mixtures were separated by preparative layer chromatography (PLC) into varying amounts of the corresponding *N*-oxides (IIa – c), minor amounts of the isoxazolinylacetophenones (IIIa – c), and the corresponding oximes (IVa – c) (Table 1).

All the other pyrylium salts (*i.e.* Id – h) which were examined under similar conditions gave high yields of the expected pyridine *N*-oxides (Table 1), and no attempts were undertaken to examine the remaining products. Interestingly, the 2,4,6-trimethylpyrylium salt (Ih) gives a good yield of the corresponding *N*-oxide in basic medium as well.[1]

In the hope of obtaining some information about the reaction mechanism, compounds XI – XIIa, A [3-4] (Chart 3) were prepared and subjected to treatment with acid. However, this led only to hydrolysis to form the corresponding "pseudobase" (1,3,5-triphenyl-2-pentene-1,5-dione). It has previously been shown that compounds XI – XII A (Chart 3) are intermediates in the formation of the isoxazolinylacetophenones.[3,4]

Table 1. Yield and physical properties of compounds IIa—h and IVa—c.

Compound	Recrystallization solvent	M.p.,°C	Yields, %		Formula	Analyses							
			from pyrylium salts [a]	from *N*-oxidation		% C		% H		% N		% Br	
						Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found
IIa	Cyclohexane	186—189	51	32	$C_{23}H_{17}NO$	85.42	85.10	5.30	5.48	4.33	4.33		
IIb	Cyclohexane	202—204	35	10	$C_{23}H_{16}NOBr$	68.65	68.60	4.01	4.13	3.48	3.36	19.86	19.79
IIc	Cyclohexane	254—256	10	5	$C_{23}H_{15}NOBr_2$	57.41	57.70	3.14	3.34	2.91	2.86	33.22	33.37
IId	Diglyme/water	188—189	83	57	$C_{24}H_{19}NO$	85.43	85.50	5.68	5.84	4.15	4.15		
IIe	Ethanol	250—251	98	42	$C_{29}H_{21}NO$	87.19	87.00	5.30	5.48	3.51	3.30		
IIf	Ethanol	298—302	88	53	$C_{29}H_{21}NO$	87.19	87.15	5.30	5.54	3.51	3.36		
IIg	Diglyme/water	245—248	97	71	$C_{35}H_{25}NO$	88.39	88.50	5.30	5.44	2.95	3.00		
IIh, H_2O	Ether	34—37	61		$C_8H_{13}NO_2$	61.91	61.52	8.44	7.93	9.03	8.93		
IVa	Cyclohexane	143—145	24		$C_{23}H_{20}N_2O_2$	77.50	77.16	5.66	5.85	7.86	7.68		
IVb	Hexane/ benzene	164—165	52		$C_{23}H_{19}N_2O_2Br$	63.46	64.12	4.40	4.54	6.44	6.12	18.36	17.82
IVc	Cyclohexane/ benzene	212—214	45		$C_{23}H_{18}N_2O_2Br_2$	53.69	53.69	3.50	3.61	5.44	5.35	31.12	30.89

[a] The yield of the compounds IIIa—c were 21 %, 9 %, and 9 %, respectively.

Identification of products. The pyridine *N*-oxides (IIa–g) were identified (IR, mixed m.p. test) by comparison with authentic samples prepared from the parent pyridines by oxidation with 3-chloroperbenzoic acid (Table 1); the 2,4,6-trimethylpyridine *N*-oxide was identical with a sample prepared according to Ref. 1. As expected, all the *N*-oxides showed strong N–O vibration absorption between 1200 and 1300 cm^{-1} in their IR spectra (Table 2).

Table 2. Characteristic ultraviolet and infrared absorptions of pyridine *N*-oxides (II).

Compound	IR (in KBr) cm^{-1}	UV[a]					
		λ_{max} mμ	log ε	λ_{max} mμ	log ε	λ_{max} mμ	log ε
IIa	1255 (N–O)	213	4.22	265	4.33	322	3.95
IIb	1250 (N–O)	214	4.38	272	4.49	314	4.37
IIc	1260 (N–O)	210	4.42	276	4.47	308sh	4.15
IId	1269 (N–O)	212	4.28	258	4.36	281sh	4.09
IIe	1280 or 1290 (N–O)	211	4.35	265	4.37	295sh	4.10
IIf	1273 or 1291 (N–O)	211	4.07	267	4.17		
IIg	1275 or 1295 (N–O)	220	4.36	260	4.33		
IIh	1235 (N–O)	219	3.93	262	3.98		

[a] IIa was recorded in cyclohexane, IIb–h were recorded in 96 % ethanol.

Table 3. Nuclear magnetic resonance spectra of pyridine *N*-oxides (II).[a]

Compound	Aromatic	Methyl
IIa	2.0–2.8	
IIb	2.1–2.8	
IIc	2.2–2.8	
IId	2.0–2.8 (16 H)	7.99 (3 H)
IIe	2.0–3.3	
IIf	2.6–3.0	
IIg	2.5–3.3	
IIh	3.05 (2 H)	7.50 (6 H) 7.73 (3 H)

[a] Spectra recorded at 60 MHz in $CDCl_3$ with tetramethylsilane as internal reference. Chemical shifts are in τ values. Relative intensities are given in parenthesis.

The UV spectra (Table 2) and the NMR spectra (Table 3) also support the structure assignment. Furthermore, all the *N*-oxides are strongly photoactive, which we regard as an inherent quality of all pyridine *N*-oxides (*e.g.* Ref. 10 and papers cited therein).*

* The photochemistry of pyridine *N*-oxides (IIe–g) is currently under examination. In each case compounds assumed to be 1,3-oxazepines [10] are formed. These compounds can be prepared in very high yields by the irradiation of IIf and IIg.[11]

The isoxazolinylacetophenones (IIIa – c) were identical with samples (IR, m.p.) prepared from the corresponding pyrylium salts and hydroxylamine in basic ethanol.[3,4]

The oximes (IVa – c) (Chart 1) were assigned their structure on the basis of the following. In the case of IVa, an identical compound (IR, m.p.) could be prepared from IIIa and hydroxylamine according to a general procedure for the formation of oximes from ketones.[12] This is regarded as important evidence for the proposed structures for compounds IVa – c. Further evidence was found in the spectra of these compounds. Their IR spectra (Table 4) show

Table 4. Characteristic ultraviolet and infrared absorptions of compounds IVa – c.

Compound	IR (in KBr) cm^{-1}	UV (in 96 % ethanol)					
		λ_{max} mμ	log ε	λ_{max} mμ	log ε	λ_{max} mμ	log ε
IVa	3233 (O–H) broad	210	4.21	255	4.02		
IVb	3327 (O–H) broad	213	4.27	265	4.31	294sh	4.05
IVc	3242 (O–H) broad	209	4.14	264	4.06	298sh	3.19

broad absorption bands in the 3300 cm^{-1} region, indicating hydrogen bonded OH groups in the compounds. The NMR spectra of IVa – c (Table 5) show the expected similarities to the parent ketones, and are thus in very good agreement with the assigned structures for IVa – c.

DISCUSSION

The primary products from the reaction between pyrylium salts and nucleophilic reagents are generally believed to be γ-pyranes (V) and/or α-pyranes (VI) (Chart 2).[14] Compounds of these types have actually been found, and it was shown that they may interconvert by allylic rearrangements.[14b]

A further reaction leading to dienones can occur from VI (which obviously is the important species in the presently considered cases; in the following discussion only products occurring from VI are discussed). Compounds of type VII have also been isolated. In the cases, as illustrated in Chart 2, where the new substituent possesses hydrogen atoms, compounds VII can react further to give VIII and/or IX. Compounds of the latter type have been isolated and characterized both in the case where the attacking nucleophilic reagent was phenylhydrazine [5–9] and where it was hydroxylamine.[3,4]

Table 5. Nuclear magnetic resonance spectra of compounds IVa–c.[a]

Compound	Solvent	Oxime proton	H_A^1	H_B^1	J_{AB}^1	H_A^2	H_B^2	J_{AB}^2	Aromatic
IVa	$CDCl_3$	1.25 (1H) broad	6.21	6.58	16.6	6.24	6.59	13.5	2.3–2.9 (15H)
IVb	$CDCl_3$	1.00 (1H) broad	6.22	6.62	16.6	6.29	6.58	13.4	2.4–2.9 (14H)
IVc	Pyridine-d_5	−3.89 (1H) broad	5.76	6.38	16.8	5.87	6.41	13.6	2.1–2.9 (13H)

[a] Spectra recorded at 60 MHz with tetramethylsilane as internal reference. Chemical shifts are in τ values, and coupling constants in Hz. The positions of the A or B parts of the AB quartets are calculated. Relative intensity given in parenthesis. Relative intensity of the AB parts is 4.

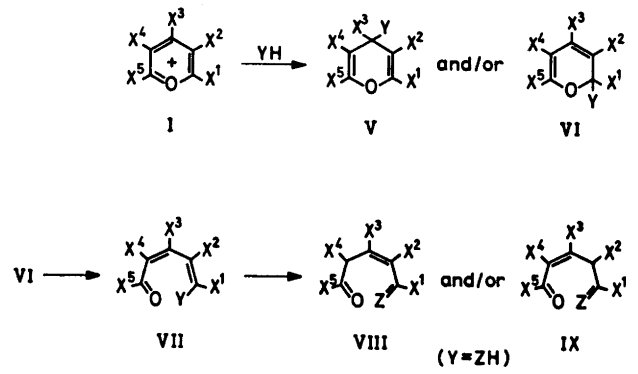


Chart 2. (As regards the meaning of X^1, X^2, *etc.*, see Chart 1.)

In order to explain the two pathways operating in the reaction of polyaryl pyrylium salts with either hydroxylamine or phenylhydrazine the following scheme (Chart 3) is tentatively proposed.

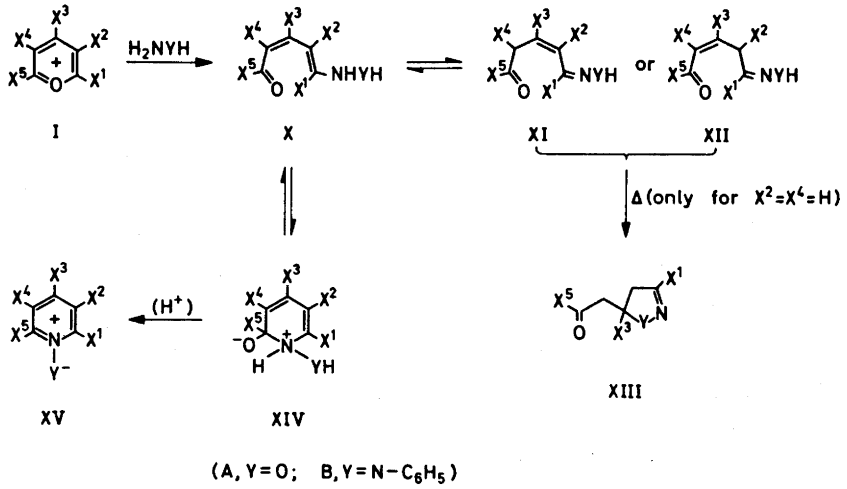


Chart 3. (As regards the meaning of X^1, X^2, *etc.*, see Chart 1.)

Compounds XI and/or XII, possibly catalyzed by base, react to give the five-membered ring compounds XIII. Base catalysis is, however, not necessary, since it has been shown that with $Y = NC_6H_5$, as well as with $Y = O$ this reaction occurs by boiling in ethanol. Only for $Y = NC_6H_5$ has it been shown [6,7] that the other reaction pathway, leading in this case to *N*-imides (XV B), takes place from XI – XII B. By treating compound XI – XIIa, A with glacial

acetic acid and sodium acetate trihydrate solely hydrolysis to 1,3,5-triphenyl-2-pentene-1,5-dione took place. However, this only indicates that the attack of nucleophilic reagents on pyrylium salts can be reversed. Under the conditions where *N*-oxides were formed, a substantial excess of hydroxylamine was present, thus advancing the forward reaction. Formation of isoxazolinyl-acetophenones has so far not been observed from pyrylium salts Id–h.

CONCLUSION

The results presented in this paper constitute a useful synthetic method for preparation of highly substituted pyridine *N*-oxides in a one-step reaction from the easily obtained corresponding pyrylium salts. The discussion links the reaction between this type of pyrylium salt and phenylhydrazine together with those of the pyrylium salts and hydroxylamine, and the proposed reaction mechanism suggests how this can be rationalized.

EXPERIMENTAL

Microanalyses were carried out in the Microanalysis Department of this laboratory by Mr. Preben Hansen and his staff.

Melting points (uncorrected) were determined on a Reichert melting point microscope or on a Büchi melting point apparatus.

Infrared spectra were recorded on a Perkin Elmer Model 337 grating infrared spectrophotometer. Ultraviolet spectra were recorded on a Perkin Elmer Model 137 UV spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian A 60 A spectrometer.

Preparative layer chromatography (PLC) was performed using 20×100 cm plates with a 2.5 mm thick layer of silica gel (Merck $PF_{254+366}$). The plates were developed 2–4 times with a mixture of benzene, petroleum ether, and acetone in the ratio 7:7:1. The fractions were isolated by continuous extraction with chloroform in a Soxhlet apparatus.

Pyrylium salts. These were prepared according to the previously reported methods: Ia–c,[13] Id–e,[15] If–g,[16] and Ih.[17]

Reaction of pyrylium salts with hydroxylamine. All these reactions were undertaken using, *e.g.*, the following procedure: 2,3,5,6-tetraphenylpyrylium bromide (2.0 g), hydroxylamine hydrochloride (1.5 g), and sodium acetate trihydrate (10 g) were added to acetic acid (40 ml). This mixture was refluxed for 5 min, after which it was poured into water (200 ml). In the subsequent purification of the crude products, various procedures were followed.

The reaction mixtures resulting from the above treatment of Ia–d were extracted with chloroform. The chloroform extracts were separated, dried over anhydrous calcium chloride, and the solvent removed *in vacuo*. The resulting oils were separated into pyridine *N*-oxides, and various byproducts by PLC (Table 1).

The 2,3,4,6-tetraphenylpyridine *N*-oxide (IIe), 2,3,5,6-tetraphenylpyridine *N*-oxide (IIf), and pentaphenylpyridine *N*-oxide (IIg) were isolated directly as crystals from the crude hydrolyzed reaction mixture by filtration and were purified by recrystallization (Table 1).

The 2,4,6-trimethylpyridine *N*-oxide (IIh) was extracted from the crude reaction mixture with chloroform. The organic phase was dried over anhydrous calcium chloride. After removal of the drying agent by filtration, and the chloroform by distillation, the *N*-oxide was purified by vacuum distillation; b.p. 72–73°, 0.5 torr. After standing for some days in a loosely stoppered vessel 2,4,6-trimethylpyridine *N*-oxide monohydrate crystallized out from the distillate.

The results from these reactions are summarized in Table 1.

Hydrolysis of compound XI–XIIa, A. Compound XI–XIIa, A (500 mg) and sodium acetate trihydrate (5.0 g) were suspended in glacial acetic acid (20 ml). This

mixture was refluxed for 1 h, after which it was poured into water (100 ml). After extraction with chloroform and evaporation of the solvent the residue was triturated with methanol and the crystals removed by filtration (nearly quantitative conversion). Recrystallization from methanol gave a compound which was identified as 1,3,5-triphenyl-1,5-pentenedione [18] (IR, m.p.).

N-Oxidation of pyridines * *with 3-chloroperbenzoic acid.* The *N*-oxides IIa–g were also prepared as exemplified in the following procedure: 2,3,5,6-tetraphenylpyridine (400 mg) and *ca.* 80 % 3-chloroperbenzoic acid (900 mg, 4 molar equivalents) were dissolved in chloroform (50 ml). The solution was left in the dark for 14 days at room temperature. After this, the solution was washed twice with 1 N sodium hydroxide, once with saturated sodium chloride, and dried over anhydrous calcium chloride. After filtration, the solvent was removed *in vacuo*, and the residue separated by PLC into: (1) 2,3,5,6-tetraphenylpyridine *N*-oxide (219 mg, ~53 %); and (2) starting material (95 mg). The *N*-oxides prepared in this manner were identical with those prepared directly from the pyrylium salts with hydroxylamine (IR, m.p.).

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* The pyridines were prepared from pyrylium salts and aqueous ammonia.[13]