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 isoxazolinylacetonophenes 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.\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{3,4} and it was shown that no formation of the corresponding amine N-oxides (II) took place. Instead the isoxazolinylacetonophenes (III) were formed via thermally unstable intermediates (XI-\text{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 (\textit{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\textsuperscript{3,5-9} to allow some general mechanistic conclusions to be drawn.

\begin{center}
\begin{tabular}{cccccc}
 & \text{X}^1 & \text{X}^2 & \text{X}^3 & \text{X}^4 & \text{Y}^- \\
\text{a} & \text{C}_2\text{H}_5 & \text{H} & \text{C}_2\text{H}_5 & \text{H} & \text{C}_2\text{H}_5 & \text{BF}_4^- \\
\text{b} & \text{C}_2\text{H}_5 & \text{H} & 4\text{-BrC}_6\text{H}_4 & \text{H} & \text{C}_2\text{H}_5 & \text{BF}_4^- \\
\text{c} & 4\text{-BrC}_6\text{H}_4 & \text{H} & \text{C}_2\text{H}_5 & \text{H} & \text{C}_2\text{H}_5 & \text{BF}_4^- \\
\text{d} & \text{C}_2\text{H}_5 & \text{CH}_3 & \text{C}_2\text{H}_5 & \text{H} & \text{C}_2\text{H}_5 & \text{ClO}_4^- \\
\text{e} & \text{C}_2\text{H}_5 & \text{C}_2\text{H}_5 & \text{C}_2\text{H}_5 & \text{CH}_3 & \text{C}_2\text{H}_5 & \text{Br}^- \\
\text{f} & \text{C}_2\text{H}_5 & \text{CH}_3 & \text{C}_2\text{H}_5 & \text{CH}_3 & \text{C}_2\text{H}_5 & \text{ClO}_4^- \\
\text{g} & \text{CH}_3 & \text{H} & \text{CH}_3 & \text{H} & \text{CH}_3 & \text{ClO}_4^- \\
\text{h} & \text{CH}_3 & \text{H} & \text{CH}_3 & \text{H} & \text{CH}_3 & \text{ClO}_4^- \\
\end{tabular}
\end{center}

\textit{Chart 1.}

An additional impetus in undertaking this work was the preparative possibilities of the reactions leading to pyridine \textit{N}-oxides. The usual preparation of polyarylpyridine \textit{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 \textit{N}-oxide. In the present method this problem is not important.

**RESULTS**

\textit{Reactions.} The reaction of 2,4,6-triarylpurple 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 \textit{N}-oxides (IIa-c), minor amounts of the isoxazolinylacetophenones (IIIa-c), and the corresponding oximes (IVa-c) (Table 1).

All the other pyrylium salts (\textit{i.e.} Id-h) which were examined under similar conditions gave high yields of the expected pyridine \textit{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 \textit{N}-oxide in basic medium as well.\textsuperscript{1}

In the hope of obtaining some information about the reaction mechanism, compounds XI-XIIa, A\textsuperscript{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.\textsuperscript{3,4}

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

<table>
<thead>
<tr>
<th>Compound</th>
<th>Recrystallization solvent</th>
<th>M.p., °C</th>
<th>Yields, %</th>
<th>Formula</th>
<th>Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>Cyclohexane</td>
<td>186–189</td>
<td>51</td>
<td>C₃H₇NO</td>
<td>% C</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Calc.</td>
</tr>
<tr>
<td>IIb</td>
<td>Cyclohexane</td>
<td>202–204</td>
<td>35</td>
<td>C₃H₇NOBr</td>
<td>% H</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Calc.</td>
</tr>
<tr>
<td>IIIc</td>
<td>Cyclohexane</td>
<td>254–256</td>
<td>10</td>
<td>C₃H₇NOBr₂</td>
<td>% N</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Calc.</td>
</tr>
<tr>
<td>IIId</td>
<td>Diglyme/water</td>
<td>188–189</td>
<td>83</td>
<td>C₃H₇NO</td>
<td>% Br</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Calc.</td>
</tr>
<tr>
<td>IIe</td>
<td>Ethanol</td>
<td>250–251</td>
<td>98</td>
<td>C₃H₇NO</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIf</td>
<td>Ethanol</td>
<td>298–302</td>
<td>88</td>
<td>C₃H₇NO</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIg</td>
<td>Diglyme/water</td>
<td>245–248</td>
<td>97</td>
<td>C₃H₇NO</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIh, H₂O</td>
<td>Ether</td>
<td>34–37</td>
<td>61</td>
<td>C₃H₇NO</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVa</td>
<td>Cyclohexane</td>
<td>143–145</td>
<td>24</td>
<td>C₃H₇NO₂O₂</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVb</td>
<td>Hexane/benzene</td>
<td>164–165</td>
<td>52</td>
<td>C₃H₇NO₂O₂Br</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVc</td>
<td>Cyclohexane/benzene</td>
<td>212–214</td>
<td>45</td>
<td>C₃H₇NO₂O₂Br</td>
<td></td>
</tr>
</tbody>
</table>

*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).

<table>
<thead>
<tr>
<th>Compound</th>
<th>IR (in KBr)</th>
<th>UVa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cm⁻¹</td>
<td>λmax mμ</td>
</tr>
<tr>
<td>IIa</td>
<td>1255 (N–O)</td>
<td>213</td>
</tr>
<tr>
<td>IIb</td>
<td>1250 (N–O)</td>
<td>214</td>
</tr>
<tr>
<td>IIc</td>
<td>1260 (N–O)</td>
<td>210</td>
</tr>
<tr>
<td>IId</td>
<td>1269 (N–O)</td>
<td>212</td>
</tr>
<tr>
<td>IIf</td>
<td>1280 or 1290 (N–O)</td>
<td>211</td>
</tr>
<tr>
<td>IIg</td>
<td>1273 or 1291 (N–O)</td>
<td>211</td>
</tr>
<tr>
<td>IIh</td>
<td>1275 or 1295 (N–O)</td>
<td>220</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Compound</th>
<th>Aromatic</th>
<th>Methyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>2.0–2.8</td>
<td>7.99 (3 H)</td>
</tr>
<tr>
<td>IIb</td>
<td>2.1–2.8</td>
<td></td>
</tr>
<tr>
<td>IIc</td>
<td>2.2–2.8</td>
<td></td>
</tr>
<tr>
<td>IId</td>
<td>2.0–2.8 (16 H)</td>
<td></td>
</tr>
<tr>
<td>IIe</td>
<td>2.0–3.3</td>
<td></td>
</tr>
<tr>
<td>IIf</td>
<td>2.6–3.0</td>
<td></td>
</tr>
<tr>
<td>IIg</td>
<td>2.5–3.3</td>
<td></td>
</tr>
<tr>
<td>IIh</td>
<td>3.05 (2 H)</td>
<td>7.50 (6 H)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(7.73 (3 H)</td>
</tr>
</tbody>
</table>

*a Spectra recorded at 60 MHz in CDCl₃ 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-oxazepines¹⁰ are formed. These compounds can be prepared in very high yields by the irradiation of IIf and IIg.¹¹

The isoxazolylacetophenones (IIIa–c) were identical with samples (IR, m.p.) prepared from the corresponding pyrylium salts and hydroxylamine in basic ethanol.\textsuperscript{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.\textsuperscript{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>
<thead>
<tr>
<th>Compound</th>
<th>IR (in KBr)</th>
<th>UV (in 96 % ethanol)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cm\textsuperscript{-1}</td>
<td>$\lambda_{\text{max}}$ m\textmu</td>
</tr>
<tr>
<td>IVA</td>
<td>3233 (O–H) broad</td>
<td>210</td>
</tr>
<tr>
<td>IVb</td>
<td>3327 (O–H) broad</td>
<td>213</td>
</tr>
<tr>
<td>IVc</td>
<td>3242 (O–H) broad</td>
<td>209</td>
</tr>
</tbody>
</table>

broad absorption bands in the 3300 cm\textsuperscript{-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 $\gamma$-pyrans (V) and/or $\alpha$-pyrans (VI) (Chart 2).\textsuperscript{14} Compounds of these types have actually been found, and it was shown that they may interconvert by allylic rearrangements.\textsuperscript{14b}

A further reaction leading to dienes 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\textsuperscript{5–9} and where it was hydroxylamine.\textsuperscript{3,4}

Table 5. Nuclear magnetic resonance spectra of compounds IVa—c.a

<table>
<thead>
<tr>
<th>Compound</th>
<th>Solvent</th>
<th>Oxime proton</th>
<th>$H_A^1$</th>
<th>$H_B^1$</th>
<th>$J_{AB}^1$</th>
<th>$H_A^2$</th>
<th>$H_B^2$</th>
<th>$J_{AB}^2$</th>
<th>Aromatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVa</td>
<td>CDCl$_4$</td>
<td>1.25 (1H) broad</td>
<td>6.21</td>
<td>6.58</td>
<td>16.6</td>
<td>6.24</td>
<td>6.59</td>
<td>13.5</td>
<td>2.3–2.9 (15H)</td>
</tr>
<tr>
<td>IVb</td>
<td>CDCl$_4$</td>
<td>1.00 (1H) broad</td>
<td>6.22</td>
<td>6.62</td>
<td>16.6</td>
<td>6.29</td>
<td>6.58</td>
<td>13.4</td>
<td>2.4–2.9 (14H)</td>
</tr>
<tr>
<td>IVc</td>
<td>Pyridine-$d_4$</td>
<td>−3.89 (1H) broad</td>
<td>5.76</td>
<td>6.38</td>
<td>16.8</td>
<td>5.87</td>
<td>6.41</td>
<td>13.6</td>
<td>2.1–2.9 (13H)</td>
</tr>
</tbody>
</table>

a Spectra recorded at 60 MHz with tetramethylsilane as internal reference. Chemical shifts are in $\tau$ 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.
PYRILYUM SALTS AND HYDROXYLAMINE

\[
\begin{align*}
\text{I} & \xrightarrow{\text{YH}} \text{V} \quad \text{and/or} \quad \text{VI} \\
\text{VI} & \xrightarrow{} \text{VIII} \quad \text{and/or} \quad \text{IX} \\
\end{align*}
\]

Chart 2. (As regards the meaning of \(X^1, X^2, \text{etc.}, \) see Chart 1.)

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

\[
\begin{align*}
\text{I} & \xrightarrow{\text{H,N,YH}} \text{X} & \text{XI} & \xrightarrow{\text{YH}} \text{XII} \\
\text{XV} & \xrightarrow{(H^+)} \text{XIV} & \text{XIII} & \Delta \text{(only for } X^2 = X^4 = \text{H)} \\
\end{align*}
\]

(A, \(Y = \text{O}; \ B, Y = \text{N}-\text{C}_6\text{H}_5\))

Chart 3. (As regards the meaning of \(X^1, X^2, \text{etc.}, \) 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 \(Y = \text{NC}_6\text{H}_5\), as well as with \(Y = \text{O}\) this reaction occurs by boiling in ethanol. Only for \(Y = \text{NC}_6\text{H}_5\) 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 – XII a, 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 pyrylum salts can be reversed. Under the condi-
tions 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 pyrylum 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 pyrylum salts. The discussion links
the reaction between this type of pyrylum salt and phenylhydrazine together
with those of the pyrylum 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 spectro-
photometer. Ultraviolet spectra were recorded on a Perkin Elmer Model 137 UV spectro-
photometer. Nuclear magnetic resonance spectra were recorded on a Varian A 60 A
spectrometer.

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

Pyrylum salts. These were prepared according to the previously reported methods:
Ia–c,12 Id–e,12 If–g,14 and Ih,17

Reaction of pyrylum salts with hydroxylamine. All these reactions were undertaken
using, e.g., the following procedure: 2,3,5,6-tetraphenylpyrylum bromide (2.0 g), hydroxyl-
amine 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 (IIIh) 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.).

\textit{N}-Oxidation of pyridines * with 3-choroperbenzoic 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 \textit{in vacuo}, and the residue separated by PLC into: (1) 2,3,5,6-tetraphenylpyridine N-oxide (219 mg, \(\sim 53 \%\)); 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.).

**REFERENCES**

5. Schneider, W. and Seebach, F. Ber. 54 (1921) 2285.
17. Diels, O. and Alder, K. Ber. 60 (1927) 716.

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* The pyridines were prepared from pyrylium salts and aqueous ammonia.\(^{13}\)