Tetrahedron, 1961, Vol. 14, pp. 151 to 160. Pergamon Press Ltd. Printed in Northern Ireland

PREPARATION AND PERACID OXIDATION OF 2-(*p*-DIMETHYLAMINO)-STYRYL-PYRIDINE

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(*Received* 20 *January* 1961)

Abstract—The title compound is obtained by reduction of its 1-oxide, prepared in fair yield by condensation of 2-picoline-1-oxide and *p*-dimethylamino-benzaldehyde in pyridine in the presence of KOH. The results of the stepwise oxidation by perbenzoic acid show that the oxygen atom adds first to the amino nitrogen, appearing to indicate that the interaction effects between the dimethylamino group and the pyridine ring are small.

In substituted pyridines electronic interaction between an electron-donor substituent and the pyridine nucleus, is greatest when the substituent is bonded directly to the nucleus, but is decreased to a surprising extent when the substituent is bonded to the pyridine through a system of conjugated double bonds.

The absorption spectra of the three *p*-dimethylamino-phenylazo-pyridines[1] are very similar; only the 4-isomer exhibits a small bathochromic shift. Examination of the absorption spectra of the isomeric phenylazopyridines,[2] very similar to each other and almost identical with that of the azobenzene, indicates the existence of a small degree of conjugation between the phenylazo-group and the pyridine nitrogen.

This report concerns the behaviour, with respect to the oxidation by organic peracids, of the 2-(*p*-dimethylamino)-styryl-pyridine, in which the —CH=CH— group is substituted for the azo group between the pyridine and the substituted-phenyl-group, and also describes a convenient method of preparation of the starting base.

The condensation of α-picoline with *p*-dimethylamino-benzaldehyde was reported by Parker and Furst[3] who effected the condensation in toluene in the presence of piperidine acetate as catalyst. They observed, however, the preferential formation of an unidentified compound corresponding to the empirical formula $C_{23}H_{27}N_3$. This same compound was obtained also not only when 2-picoline base was replaced by its 1-oxide, but even when no heterocyclic was used in the reaction. Apparently, this compound is formed from the condensation of the aldehyde with piperidine under the conditions used by the above.

By the condensation of *p*-dimethylamino-benzaldehyde with 2-picoline-1-oxide, the above authors obtained (together with the unidentified product) 2-(*p*-dimethylamino)-styryl-pyridine-1-oxide, isolated with difficulty and in a maximum yield of 13 per cent after 47 hours of reaction time.

Jerchel *et al.*,[4] studying the reaction between α-picoline and benzaldehyde, stated that the reaction is best carried out in a mixture of a mole of acetic anhydride and a mole of acetic acid per mole of picoline and 1·2 moles of benzaldehyde, with exclusion

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[1] L. Pentimalli, *Tetrahedron* **9**, 194 (1960).
[2] L. Pentimalli, *Gazz. Chim. ital.* **90**, 1203 (1960).
[3] E. D. Parker and A. Furst, *J. Org. Chem.* **23**, 201 (1958).
[4] D. Jerchel and H. E. Heck, *Liebigs Ann.* **613**, 171 (1958).

of air. In basic medium, on the other hand, the best results were obtained in methanol, by the addition of 0·2 mole of piperidine per mole of picoline derivative and 1·4 moles of benzaldehyde. With piperidine acetate or potassium acetate, as condensing agents, the yields decrease. Furthermore, Jerchel *et al.*[4] stated that 2- and 4-picoline undergo condensation only in acidic medium.

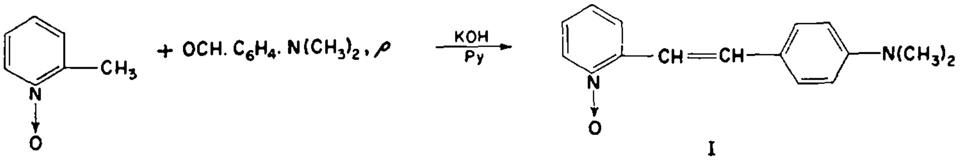
If the picoline 1-oxides and benzaldehyde are allowed to react in acidic medium, no condensation occurs. In methanol or s-butanol, in the presence of piperidine, only N,N′-benzylidene-di-piperidine is formed. The styryl-pyridine 1-oxides are obtained instead from 2- and 4-picoline 1-oxides with potassium methoxide in methanol, in 56 per cent yield,[4] according to an earlier method by Katritzky,[5] who obtained 2-styryl-pyridine-1-oxide in 22 per cent yield.

Katritzky also prepared[6] in the γ-series, 4-(*p*-dimethylamino)-styryl-pyridine (12 per cent yield) by condensation in acidic medium, of aldehyde (0·08 mole) with 4-picoline (0·08 mole) in acetic anhydride (0·20 mole) by a 30 hours reflux under nitrogen, and 4-(*p*-dimethylamino)-styryl-pyridine-1-oxide (11 per cent yield) from 4-picoline-1-oxide and *p*-dimethylamino-benzaldehyde, by the above method.[5]

Our research has allowed the development of a method of preparation of the 2-(*p*-dimethylamino)-styryl-pyridine by reduction of its 1-oxide, obtained (in fair yield) by condensation in basic medium.

The condensation of the picoline base with aromatic aldehydes occurs, as mentioned, in acidic medium; in the case of *p*-dimethylamino-benzaldehyde, whose reactivity is often particularly low, the maximum yields are little better than 10 per cent. The use of additional catalysts, of other stronger acids, or of more vigorous conditions, does not improve the results and often leads only to resinous products without recovery of the starting materials.

The condensation of the picoline 1-oxide, which we have seen gives rather low yields with potassium methoxide in methanol, is effected much better, as we have found, in anhydrous pyridine in the presence of powdered potassium hydroxide, under a 3–6 hour reflux. From 4-picoline-1-oxide and *p*-dimethylamino-benzaldehyde, 4-(*p*-dimethylamino)-styryl-pyridine-1-oxide was obtained in 78 per cent yield after 3 hours of reflux. From 2-picoline-1-oxide and aldehyde the corresponding 2-styryl-derivative I was obtained in 56 per cent yield. Yields are generally lower with 2-picoline than with the 4-isomer.[4]



I

The separation of the styryl derivative is readily carried out by decomposing the reaction mixture with water and washing the formed precipitate with a little cold acetone. In the condensation with KOH, in the presence or absence of piperidine, secondary products were not apparent.

By treating the N-oxide with iron and acetic acid at 100°,[7] only oxygen is lost and

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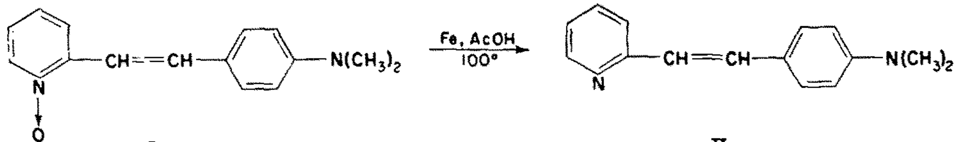
[5] A. R. Katritzky and A. M. Monro, *J. Chem. Soc.* 150 (1958).

[6] A. R. Katritzky, D. J. Short and A. J. Boulton, *J. Chem. Soc.* 1516 (1960).

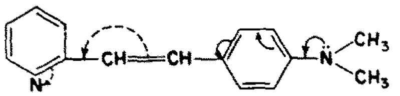
[7] H. J. den Hertog, *Rec. Trav. Chim.* 69, 472 (1950), 4-amino-pyridine from 4-nitro-1-oxide.



I II

2-(*p*-dimethylamino)-styryl-pyridine II is thus formed in 50–60 per cent yield. The ethylenic double bond, therefore, remains intact, which is different from the observation with the 1,2-bis-α-quinolyl-ethylene N,N′-dioxide, whose olefinic bond is reduced yielding 1,2-bis-α-quinolil ethane, under these conditions.[8]

Peracid oxidation of this styryl derivative was studied because, also in this case, the relative electron density on the amino– and pyridine–nitrogens will depend on the extent of the electronic interaction through the conjugated chain.



The experimental results indicate that for mono-oxidation of the 2-styryl-derivative an almost colourless compound is obtained to which must be assigned the amino oxide structure on the basis of U.V. absorption.

The 2-(*p*-dimethylamino)-styryl-pyridine base presents (Fig. 1) an intense main band at 368 mμ due to the conjugation of the dimethylamino group with the rest of the molecule. In strongly acidic medium both pyridine– and amino–nitrogens undergo protonation. The protonation of the dimethylamino group impedes the conjugative interaction of the substituent and the absorption decreases, assuming spectral

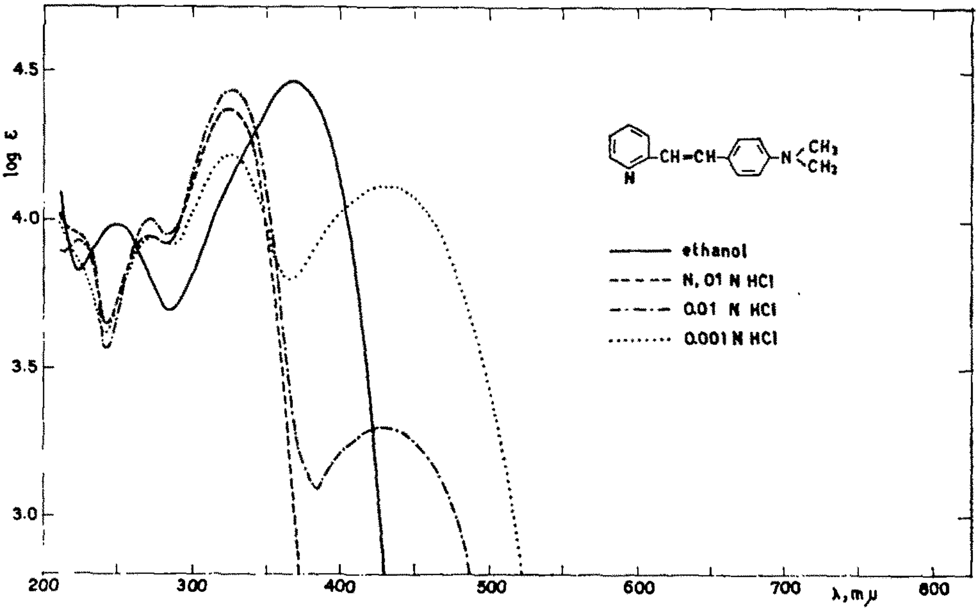


Fig. 1.

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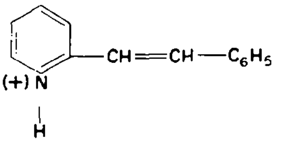
[8] M. Colonna, *Gazz. Chim. Ital.* **90**, 1179 (1960).

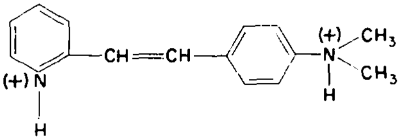
characteristics of the 2-styryl-pyridine in acidic medium. In the case of the protonated amino-derivative the absorption is even lower than that of the 2-styryl-pyridine in acidic medium since, in the latter, the conjugation of the styryl group was conditioned by the N-protonation, while in the former the electron withdrawing effect of the quaternary nitrogens at the extremes of the chain opposes the individual effect of each.

Table 1. Maxima wavelength (mμ) and corresponding intensities ($\log \varepsilon$) in the absorption spectra of 2-(*p*-dimethylamino)-styryl-pyridine in ethanol and in aqueous-ethanolic HCl

	λ_1	λ_2	λ_3	λ_4
2-(*p*-dimethylamino)-styryl-pyridine	250(3·98)	—	368(4·46)	—
2-(*p*-dimethylamino)-styryl-pyridine N, 0·1 N HCl	224~	272(3·94)	324(4·37)	—
2-(*p*-dimethylamino)-styryl-pyridine 0·01 N HCl	224(3·92)	272(3·99)	324(4·43)	424(3·30)
2-(*p*-dimethylamino)-styryl-pyridine 0·001 N HCl	224~	272(3·94)	324(4·22)	424(4·11)
2-styryl-pyridine	228(4·02)	—	310(4·40)	—
2-styryl-pyridine N HCl	...	280(3·91)	336(4·42)	—

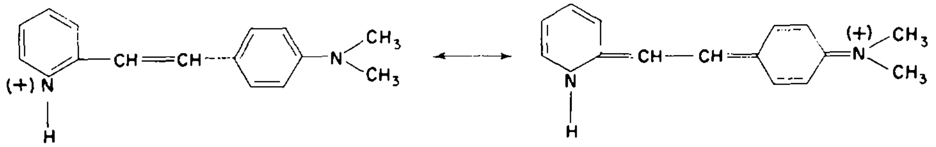


III



IV

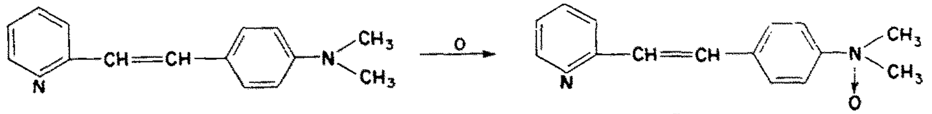
In weakly acidic medium an equilibrium between the bis-cation IV and the mono-cation V at the pyridine nitrogen occurs, which shifts toward the mono-cation as the acid concentration decreases, as shown by the bathochromic shift of the spectrum with respect to that of the free base in ethanol. Protonation at the pyridine nitrogen rather than that at the amino nitrogen is due to the higher resonance stabilisation.



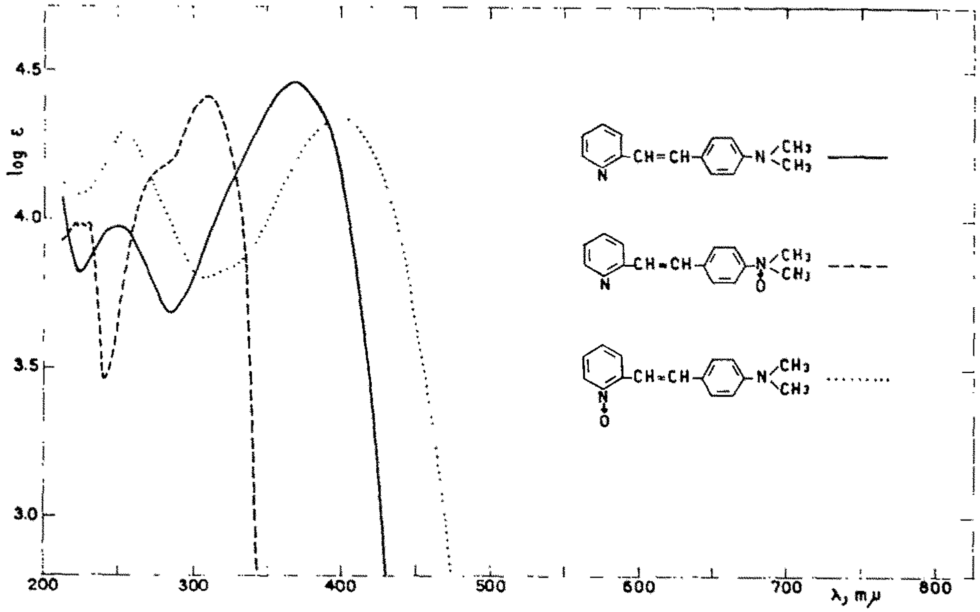
V

The product of mono-oxidation presents a spectrum (Figs. 2 and 3) almost identical to that of the unsubstituted 2-styryl-pyridine, giving evidence that here also the conjugative effect of the substituent has disappeared. In acidic medium there is a bathochromic shift, as observed with the 2-styryl-pyridine. This clearly shows, then, that the first oxygen atom is bonded to the amino-nitrogen rather than the pyridine nitrogen.

No solvent effect has been found; the mono-oxidation, performed either in chloroform or in carbon tetrachloride, always led to the same results.


CH=CH
N
CH₃
O
CH₃

VI


4.5
4.0
3.5
3.0
log ε
200
300
400
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λ, mμ
CH=CH
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CH₃
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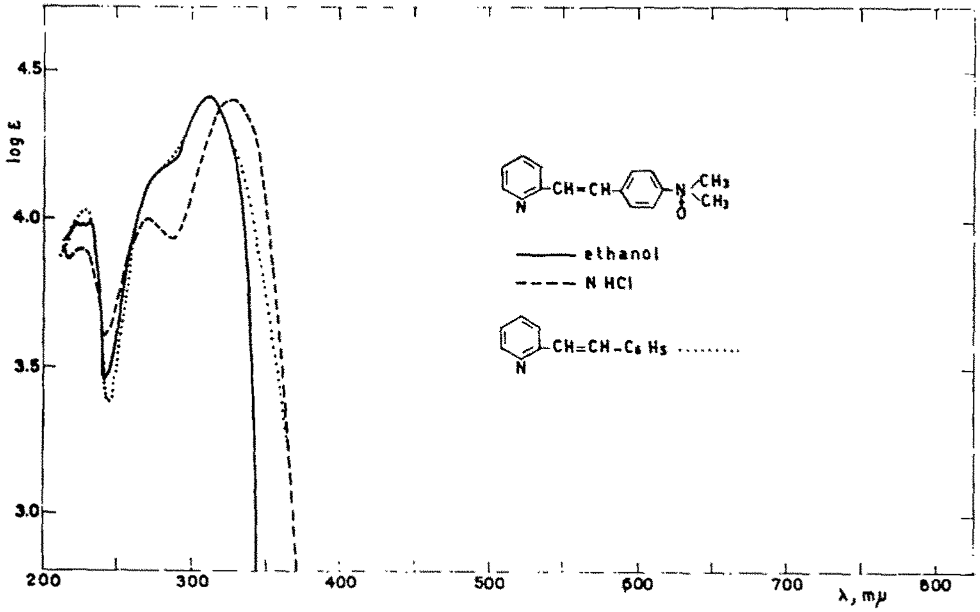
FIG. 2.


4.5
4.0
3.5
3.0
log ε
200
300
400
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λ, mμ
CH=CH
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CH₃
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ethanol
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CH=CH-C₆H₅

FIG. 3.

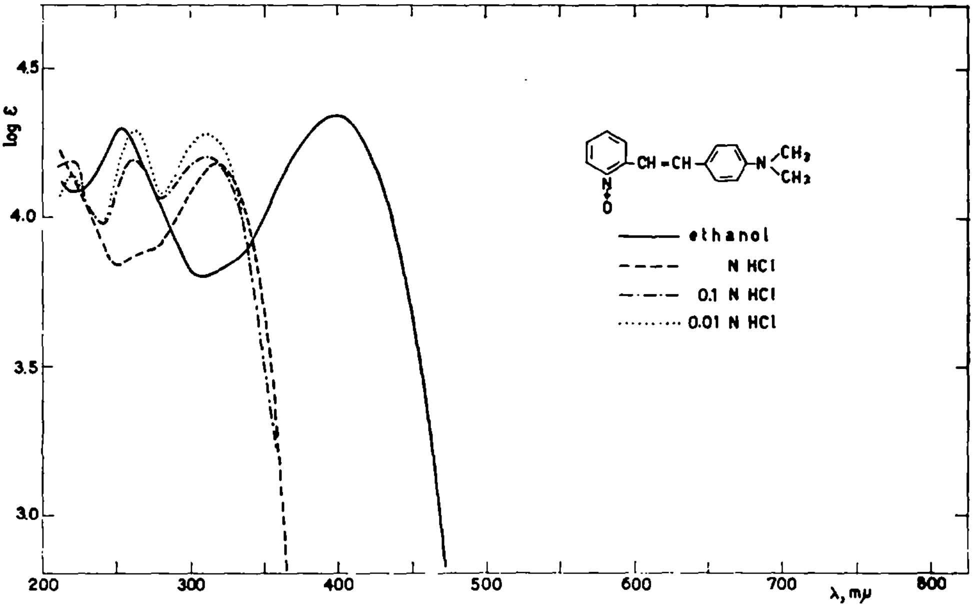


Fig. 4.

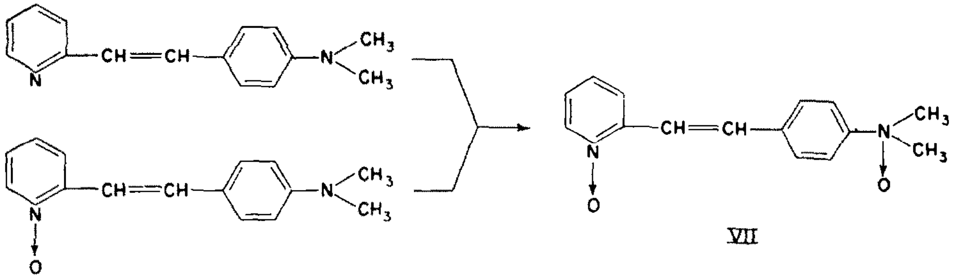
Table 2. Maxima wavelength (mμ) and corresponding intensities (log ε) in the absorption spectra of 2-(p-dimethylamino)-styryl-pyridine and related N-oxides in ethanol

	λ_1	λ_2	λ_3
2-(p-dimethylamino)-styryl-pyridine	250(3·98)	—	368(4·46)
2-(p-dimethylamino)-styryl-pyridine 1-oxide	252(4·30)		398(4·34)
2-(p-dimethylamino)-styryl-pyridine amino-oxide	226(3·98)	—	310(4·41)
2-(p-dimethylamino)-styryl-pyridine bis-oxide	232(3·96)	270(4·34)	318(4·39)
2-styryl-pyridine	228(4·02)	—	310(4·40)
2-styryl-pyridine 1-oxide	...	272(4·31)	320(4·38)

Table 3. Maxima wavelength (mμ) and corresponding intensities (log ε) in the absorption spectra of 2-(p-dimethylamino)-styryl-pyridine-1-oxide in ethanol and in aqueous-ethanolic HCl

	λ_1	λ_2	λ_3
2-(p-dimethylamino)-styryl-pyridine-1-oxide	252(4·30)		398(4·34)
2-(p-dimethylamino)-styryl-pyridine-1-oxide 0·01 N HCl	220(4·14)	262(4·29)	312(4·28)
2-(p-dimethylamino)-styryl-pyridine-1-oxide 0·1 N HCl	218(4·18)	260(4·19)	312(4·20)
2-(p-dimethylamino)-styryl-pyridine-1-oxide N HCl	...	—	318(4·17)

The 1-oxide derivative, prepared by direct synthesis, presents instead (Figs. 2 and 4) a bathochromic shift of the main band, as is the general case with conjugated substituted pyridine 1-oxides. The characteristic band of the pyridine 1-oxide group (usually at 260–270 mμ) probably remains masked by the broad band in the same



VII

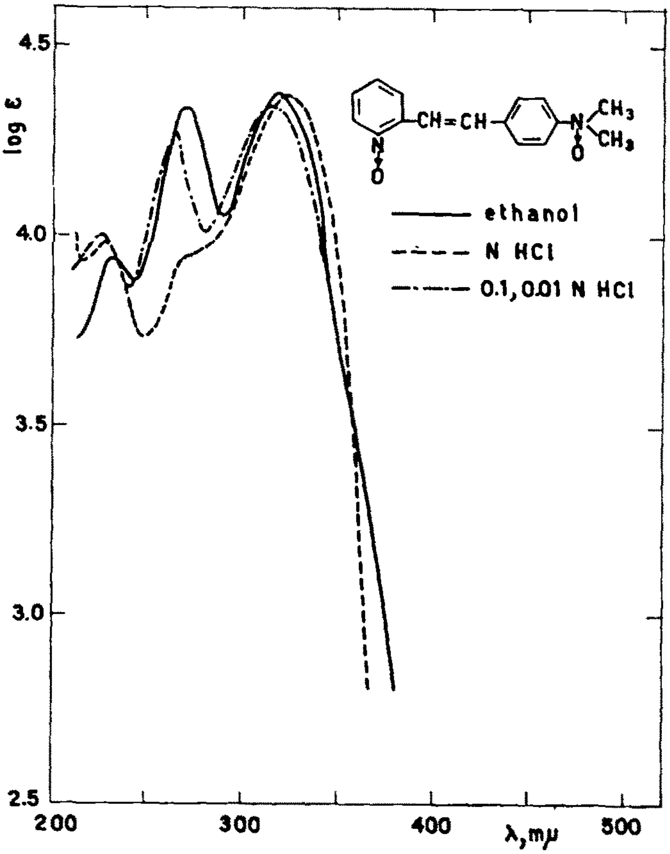


Fig. 5.

region, with λ_{max} at 252 mμ. In 0·01 N HCl the dimethylamino group is protonated, with subsequent disappearence of the electronic interaction of the substituent and corresponding reversion of the absorption curve to that of the unsubstituted 2-styrylpyridine 1-oxide (Fig. 7).

As acidity is increased even the N → O group tends to become protonated, indicated by a weakening of the original conjugation band which completely disappears in N HCl, as is the general case with aromatic N-oxides.

The product of bis-oxidation, obtained by complete oxidation either of the base or mono-oxide, contains two atoms of oxygen, one bonded to the amino–nitrogen and the other to the pyridine-nitrogen. Indeed (Fig. 5), the λ_{max} of conjugation in the higher wavelength region corresponds to that of the unsubstituted 2-styryl-pyridine (Fig. 6) and, moreover, the new band at 270 mμ, corresponding to that observed with pyridine N-oxides, is reduced to a mere inflection in strongly acidic medium.

From the results of the step-wise oxidation of the 2-(*p*-dimethylamino)-styryl-pyridine it is concluded that the first oxygen atom is bonded only to the amino-nitrogen and the second oxygen to the pyridine-nitrogen. Here also, therefore, as seen before in the corresponding azo-derivative, the electron density remains highest at the amino-nitrogen relative to that at the pyridine-nitrogen. Katritzky[9] showed, on the other hand, that for the styryl- and ethynyl-derivatives the interaction effects between the substituent and the pyridine ring are small in every case with respect to the effects observed[10] for the substituents directly bonded to the pyridine ring.

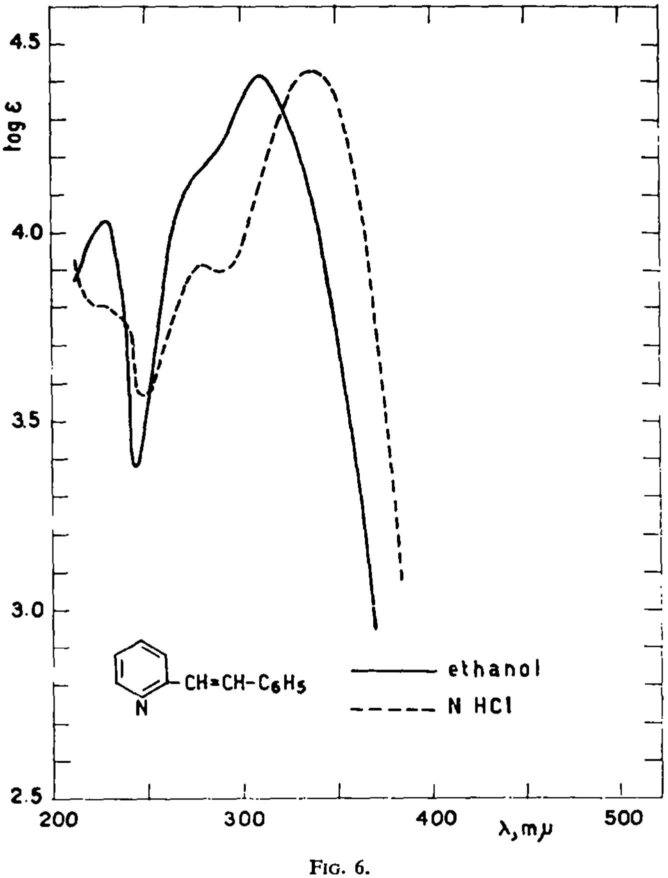


FIG. 6.

EXPERIMENTAL

2-(p-Dimethylamino)styryl-pyridine 1-oxide (I). A solution of 2-picoline 1-oxide (2·2 g, 0·020 mole) and *p*-dimethylamino-benzaldehyde (4·3 g, 0·028 mole) in anhydrous pyridine (6 ml) was added with potassium hydroxide (1·0 g) and gently refluxed for 6 hr; yellow crystals separated on the walls of the

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[9] A. R. Katritzky and P. Simmons, *J. Chem. Soc.* 1511 (1960).

[10] H. H. Jaffé and G. O. Doak, *J. Amer. Chem. Soc.* 77, 4441 (1955).

flask. The mixture was cooled, poured into cold water (100 ml) and stirred for 20 min. The brown precipitate was collected, washed with water, dried, shaken with cold acetone (30 ml) and filtered, yielding bright yellow long needles (ethanol), 2·8 g (yield 57 %), m.p. 200–201° (lit.[a]: 200–201°).

2-(p-*Dimethylamino)-styryl-pyridine* (II). To the dark-red solution of I (4 g) in glacial acetic acid (80 ml), at 90°, iron powder (6 g) was gradually added, under vigorous stirring, during 20 min, keeping the temperature at 100°. Fifteen minutes after the completion of the addition, the mixture was cooled and made strongly alkaline by the addition of aqueous NaOH. The precipitate was collected, washed with water, dried, powdered, extracted with hot benzene (two 50 ml portions) and the benzene evaporated: crude residue, m.p. 136–138°. Recrystallization (methanol) afforded 2·2 g (yield 60%), m.p. 139° (lit.[a]: 142–143°).

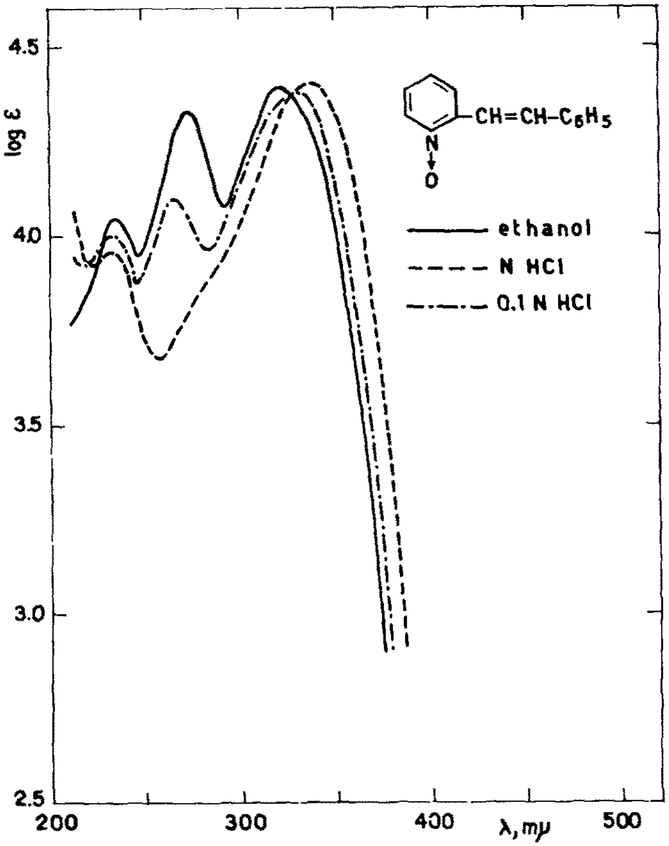

FIG. 7.

Mono-oxidation of II. To a solution of II (1·0 g) in chloroform (8 ml), at 15°, a solution of perbenzoic acid (0·7 g, 1·2 moles) in chloroform was slowly added. After standing overnight the peracid was completely reacted, and the mixture was shaken with saturated sodium carbonate solution, dried (anhydrous sodium carbonate), filtered and the chloroform evaporated. Shining colourless plates (benzene), m.p. 100° dec. (Found: N, 10·34; Calc. for $C_{15}H_{16}N_2O$: N, 10·14%), identified as 2-(*p*-dimethylamino-N-oxide)-styryl-pyridine (VI).

The same procedure was followed in carrying out the reaction in carbon tetrachloride, with exclusion of chloroform from the reaction mixture. Only the above amino oxide was isolated and characterized.

Bis-oxidation of II. To a solution of II (1·0 g) in chloroform (10 ml), at 15°, a solution of perbenzoic acid (1·7 g, 3 moles) in chloroform was slowly added. By the above procedure, 2-(*p*-dimethylamino-N-oxide)-styryl-pyridine-1-oxide (VII), light yellow prisms (pyridine), m.p. 148°, was obtained (Found: N, 9·60; Calc. for $C_{15}H_{16}N_2O_2$: N, 9·58%).

Oxidation of I. To a solution of I (4 g) in chloroform (40 ml), at 15°, a solution of perbenzoic acid (2·76 g, 1·2 moles) in chloroform was slowly added. By the above procedure, yellow prisms (pyridine), m.p. 148°, were obtained, found identical with the bis-oxide VII.

2-*Styryl-pyridine*. Prepared by condensation of α-picoline (4·7 g, 1 mole) and benzaldehyde (4·6 g, 1·2 moles) in glacial acetic acid (2·9 ml) and acetic anhydride (4·8 ml).[4] White plates (ligroin b.p. 60–80°) m.p. 89–90° (lit.[4]: 89–90°) were obtained.

2-*Styryl-pyridine*-1-*oxide*. Prepared (1) by condensation of 2-picoline-1-oxide (2·2 g, 0·020 mole) and benzaldehyde (3 g, 1·2 moles) with potassium methoxide (5 ml of a 10% methanolic solution) in methanol (5 ml)[4] or (2) by oxidation of the base (7·2 g) by 36% hydrogen peroxide (6·3 ml) in glacial acetic acid (25·7 ml).[4,5] Almost colourless prisms (benzene) were obtained, m.p. 162–163° (lit.[4]: 162–163°).

Ultra-violet-visible absorption spectra. The absorption spectra were determined in 95% ethanol and aqueous-ethanolic HCl with a Beckman Model DU Quartz spectrophotometer.