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THE REACTION OF THE ISOXAZOLINO-PYRIDINIUM CATION WITH AMINES*

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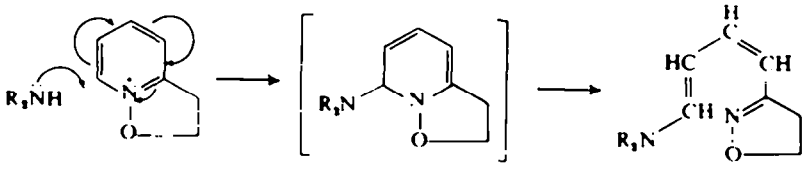
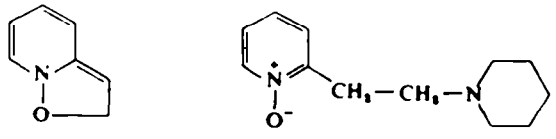
Abstract—Piperidine and dimethylamine are shown to react with the isoxazolinopyridinium cation I to yield 2-ω-aminobutadienyl-isoxazolines of type III. The amino adducts undergo protonation to yield at least three and probably four distinct protonated species (XIV, XV, XVI and XIIIa) under different conditions of acidity. The structures and further transformations of these species are determined by a combination of NMR, UV and IR spectroscopy. Hydrogenation of the adducts results in complex mixtures from which two components have been isolated and identified.



I II III

BOEKELHEIDE *et al.*[1,2] investigated the behaviour of the isoxazolinopyridinium cation I with bases, and found that reaction with piperidine yielded two crystalline products. They suggested that these were formed by initial deprotonation of I and reaction of the intermediate IV to give the N-oxide V and the adduct II. In connection with our previous interest in the reactions of 1-alkoxypyridinium salts,[3] we have reinvestigated this reaction. We obtained the product with the properties described by the previous workers for structure II, but we now show that this should be formulated as the ring-opened derivative III[$R_2 = (CH_2)_5$], although it is probably formed *via* II as an intermediate. A similar derivative III (R = Me) is obtained by reaction with dimethylamine.

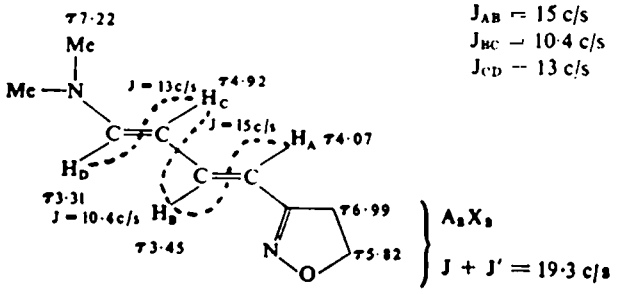
NMR *and* UV *Spectra of initial adducts.* The NMR spectra of the dimethylamine VI (Fig. 1) and piperidine adducts VII, measured at 60 Mc/s in $(CD_3)_2SO$ as solvent offer convincing evidence for their structures. In particular, the values for the vinyl



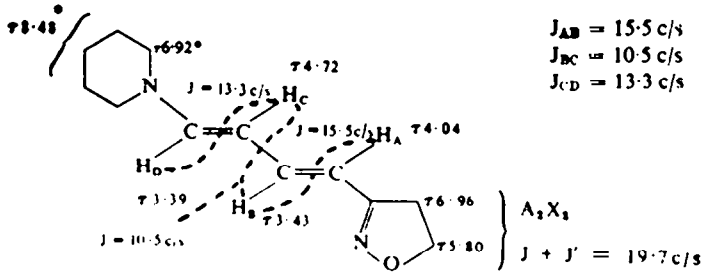
IV V

* Part XXX in the series N-*Oxides and Related Compounds*—Part XXIX. M. Ionescu, A. R. Katritzky and B. Ternai, *Tetrahedron* **22**, 3227 (1966).

[1] V. Boekelheide and W. Feely, *J. Am. Chem. Soc.* **80**, 2217 (1958).
[2] V. Boekelheide and R. Scharrer, *J. Org. Chem.* **26**, 3802 (1961).
[3] R. S. Eisenthal and A. R. Katritzky, *Tetrahedron* **21**, 2205 (1965) and Refs. therein.



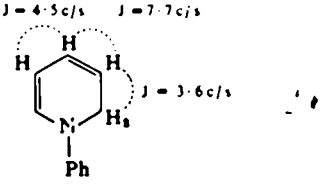
VI



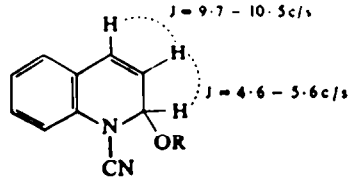
* Broad singlets.

VII

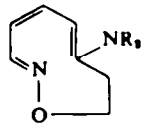
proton coupling constants are in good accord with the results of Bothner-By and Harris,[4] who examined *trans-trans* butadienes and quote J 13·1–17·7 c/s for the *trans* double bonds and J 10·4–11·3 c/s for the 2,3-single bond (cf. Refs 5–7). They are clearly not compatible with a structure of type IV (for which VIII[8] and IX[8] are useful models), and also eliminate structures X and XI for which rational mechanisms of formation can also be derived.



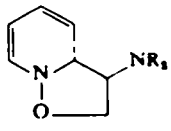
VIII



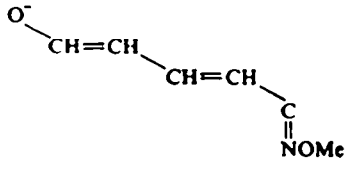
IX



X



XI



XII

[4] A. A. Bothner-By and R. K. Harris, *J. Am. Chem. Soc.* 87, 3445, 3451 (1965).
[5] J. A. Elvidge and P. D. Ralph, *J. Chem. Soc.* C, 387 (1966).
[6] R. Braimley and M. D. Johnson, *J. Chem. Soc.* 1372 (1965).
[7] B. J. Huckings and M. D. Johnson, *J. Chem. Soc.* B, 63 (1966).
[8] M. Saunders and E. H. Gold, *J. Org. Chem.* 27, 1439 (1962).

The UV spectra are in good agreement with structures VI: (λ_{max} 247, 341 mμ; ε 3020, 45800) and VII: (λ_{max}, 238, 343 mμ; ε_{max} 2900, 43000). Thus glutaconic dialdehyde sodium salt has λ_{max} 363 and a further model is XII with λ_{max} 343.[8] In contrast, (unconjugated) 1,2-dihydro-1-methyl-2-phenylpyridine has λ_{max} 286 mμ.[9]

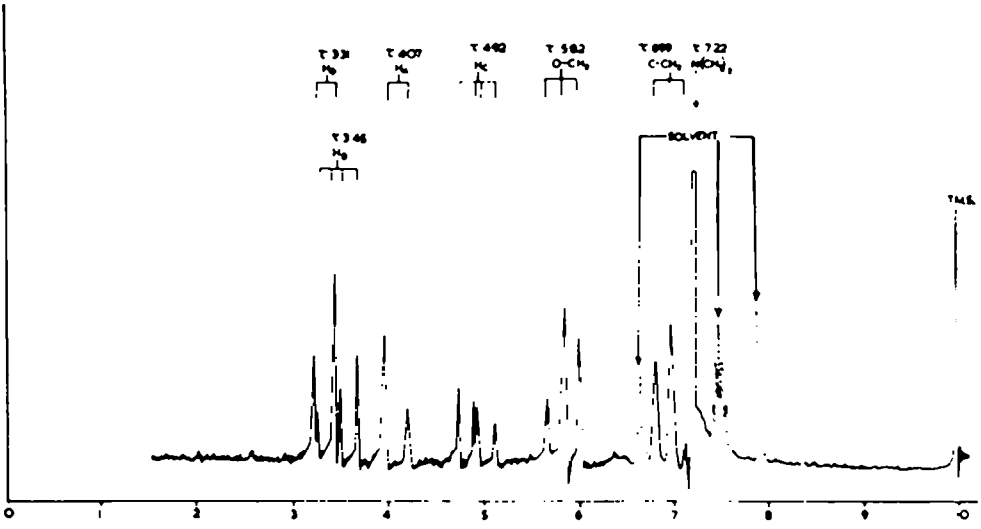


FIG. 1. NMR spectrum (60 Mc/s) of dimethylamine adduct in d_6-dimethylsulphoxide.

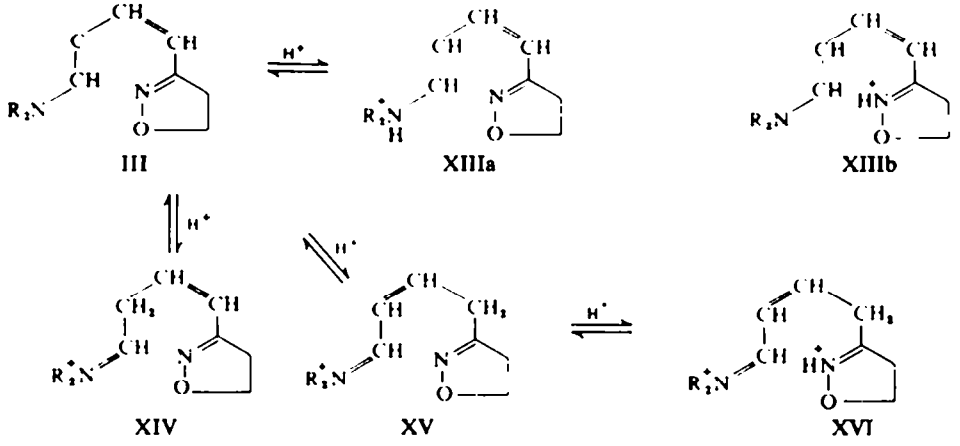
Reactions of adducts with acids. Reaction of the adducts III with acids eventually yields the cyclic cation I together with piperidine or dimethylamine. For the reaction of the piperidine adduct with hydrobromic acid, this was proved by the isolation of the cyclic cation I as the perchlorate and piperidine as the hydrobromide. This result is confirmed by the NMR and UV spectra as is discussed below. The complex course of the cyclization has been investigated spectroscopically and our interpretation is summarized in Reaction Scheme A.

The adducts III may be considered as a type of dienamine. Opitz and Merz[10] showed that dienamines with strong acids gave δ-protonated cations XXI (sometimes via N-protonation, XIX). However, weak acids caused initial protonation at the β-position, the β-protonated cation XX then isomerizing more slowly to XXI.[10] Other workers have reached similar conclusions with regard to the protonation of steroidal dienamines[11] and of the dienamine chain in dihydropyridines.[12]

Preferential initial protonation at the β- rather than the δ-position by a catalytic amount of sulphuric acid (conditions of weak acidity) was demonstrated by treating the piperidine adduct III with 0·14 equivalent of 2·8N deuterosulphuric acid (D_2SO_4-D_2O) in perdeuterodimethylsulphoxide: the observed spectrum (Fig. 2) may be compared with that of the piperidine adduct itself (Fig. 2A) (cf. structure VII) and indicates formation of the monodeutero compound XXII.

[8] R. Grashey and R. Huisgen, *Chem. Ber.* **92**, 2641 (1959).
[10] G. Opitz and W. Merz, *Liebigs Ann.* **652**, 139, 158, 163 (1962).
[11] J. A. Marshall and W. S. Johnson, *J. Org. Chem.* **28**, 421 (1963).
[12] P. S. Anderson and R. E. Lyle, *Tetrahedron Letters* 153 (1964).

Reaction Scheme A

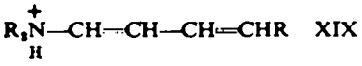


III XIIIa XIIIb

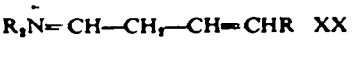
XIV XV XVI

XVII XVIII

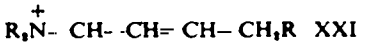
I



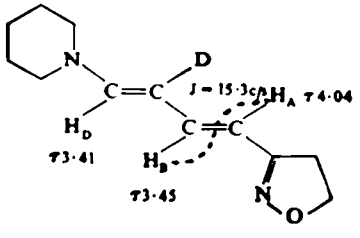
XIX



XX



XXI



XXII

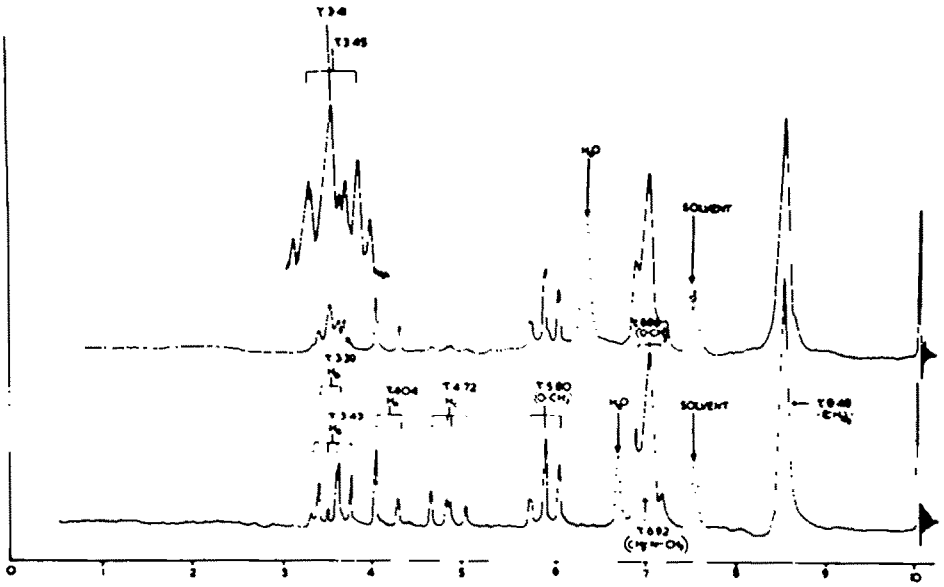
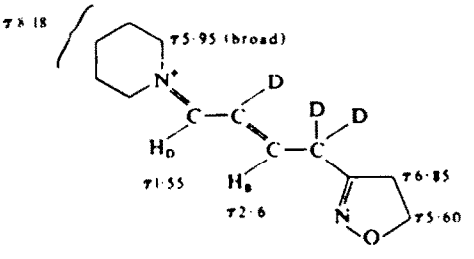


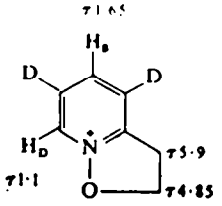
FIG. 2. NMR spectra (60 Mc/s) of piperidine adduct in d_6-dimethylsulphoxide: (A) before addition of 0·15 equiv of deuterosulphuric acid; (B) after addition of 0·15 equiv of deuterosulphuric acid.

The reaction path was further elucidated by following the NMR spectrum of the piperidine adduct in an excess of 2·8N deuterosulphuric acid. The initial spectra (Fig. 3A) disclosed the formation of the trideuterated cation XXIII with assignments as shown. Compared with VII, the considerable downfield shift of the α-piperidine proton is noteworthy, whereas the isoxazoline protons are but little displaced, indicating that protonation of the isoxazoline nitrogen is not important at this acidity [according to Quilico[13] 2-isoxazolines are weak bases, only slightly stronger than the corresponding isoxazoles (pK_a −2 to +1)]. The assignment of a cation of a structure of type XV rather than XIV is based on the low field shift of *both* the vinyl protons. On standing, the spectrum gradually changed to that (Fig. 3B) of a mixture of the selectively dideuterated bicyclic cation XXIV and piperidinium cation XXV.

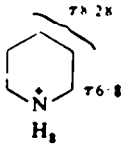


XXIII

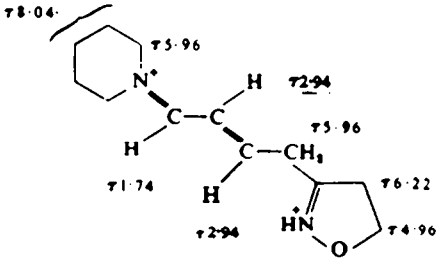
[13] A. Quilico, *Five and Six Membered Compounds with Nitrogen and Oxygen* (Edited R. H. Wiley) p. 102. Interscience, London (1962).



XXIV



XXV



XXVI

In 50% deuterosulphuric acid formation of XXIV and XXV was rapid and their NMR spectra were observed at once. In 50% sulphuric acid or trifluoroacetic acid, the spectra of the bicyclic cation I and XXV were disclosed. It was found that solutions of the bicyclic cation as a bromide I showed identical NMR spectra in 50% sulphuric acid and 50% deuterosulphuric acid, and that deuterium exchange of the bicyclic cation did not occur under these conditions.

However, behaviour in 98% sulphuric acid was again different. When the adduct III was added slowly in the absence of moisture to the concentrated acid, the NMR spectrum formed (Fig. 4) was that of the diprotonated species XXVI. This structural assignment is supported by comparison of the spectrum with that of the intermediate XXIII obtained by reaction with 2·8N sulphuric acid, and is confirmed by the UV spectra reported below. The NMR spectrum of XXVI does not change appreciably with time (Fig. 4), indicating that, as would be expected, the dication XVI is resistant to cyclization.

The earlier workers reported[1,2] that the addition of dilute mineral acid to the adduct III in ethanol irreversibly destroyed the UV spectrum and caused a new maximum at 248 mμ (ε 15,000). We find that this maximum does appear, and assign it to species XV. 1-(Piperidin-1-yl)buta-1,3-diene hydrochloride[10] has a large λ_{max} at 250 mμ (ε 8,900). In 0·2N-(Fig. 5), 2N-(Fig. 6) and 14N-(Fig. 7) sulphuric acid the extinction at 248 mμ fell away at a rate which increased with acid concentration as was also shown for mixtures of 2N-and 14N-acid with ethanol (Fig. 8), to give final spectra which were those of the cyclic cation I (Fig. 7B). However, in 98% sulphuric acid the 248 mμ peak persisted: we attribute this behaviour to the formation of the diprotonated species XVI in agreement with the NMR results discussed above. Further, in mixtures of 0·01M-acetate buffer of pH 4·9 and ethanol the initial spectrum showed, in addition to a strong maximum at 247 mμ a small peak at 290 mμ, which rapidly decreased with an increase of the 247 mμ absorption maximum (Fig. 9). The maximum at 290 mμ probably corresponds to the transient existence of the N-protonated

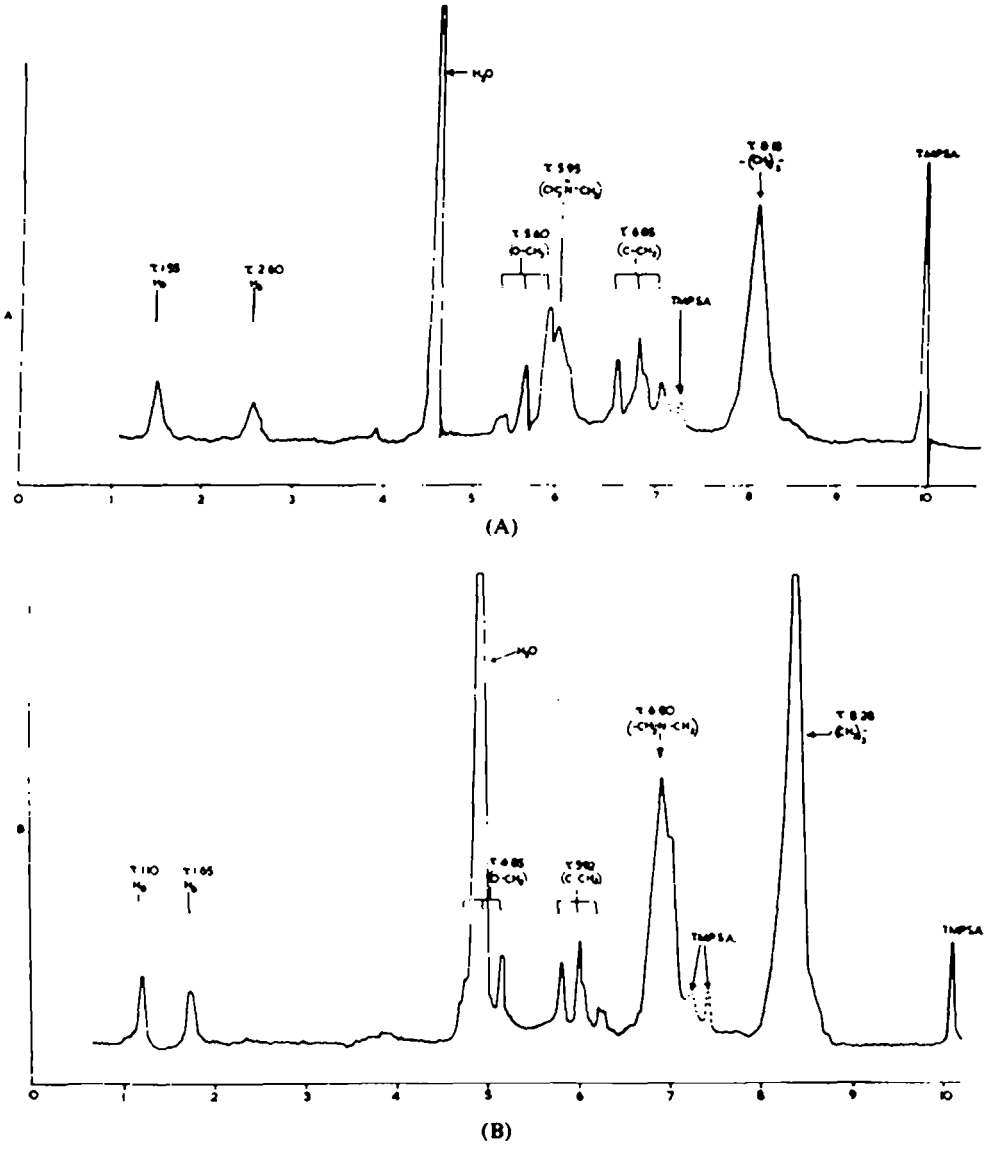


FIG. 3. NMR spectra (40 Mc/s) of reaction of piperidine adduct with excess 2·8N deuterosulphuric acid after (A) 10 min; (B) 21 hr.

species XIIIa; thus, the ketone $CH_3CH{:}CH.CH{:}CH.COCH_3$ has λ_{max} 271 mμ, and by analogy with the aryl series,[14] the corresponding isoxazoline would be expected to absorb at ca. 20 mμ longer wavelengths than this.

The development of a peak at ca. 290 mμ was also observed in mixtures of 0·2N H_2SO_4 with ethanol (and also in dioxan), where its formation was associated with an initial abnormally fast decline in the absorption at 248 mμ, followed by the usual

[14] Z.-Y. Kyi and W. Wilson, *J. Chem. Soc.* 798 (1953).

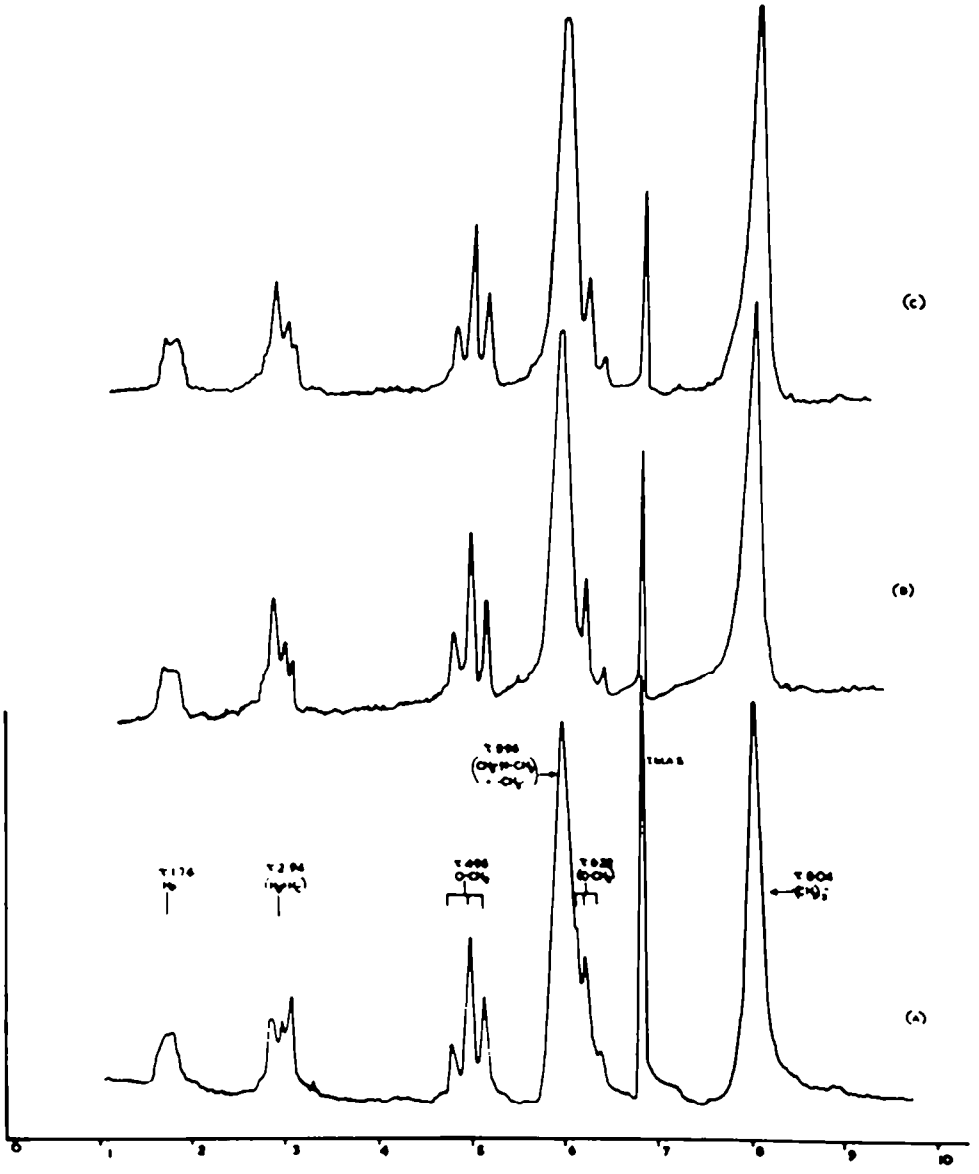
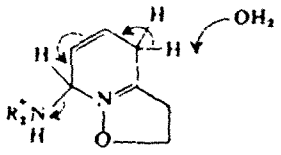


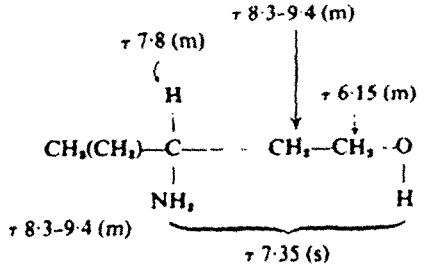
FIG. 4. NMR spectra (60 Mc/s) of piperidine adduct in conc sulphuric acid after (A) 1 hr; (B) 4½ hr; (C) 24 hr.

slow fall (Fig. 8). This behaviour may also be associated with the establishment of the initial protonation equilibrium.

The increased rate of formation of I as acid strength increased probably reflects the mechanism of the final rate-determining elimination (XVIII → V) which occurs through a small concentration of the diprotonated species XXVII. The rate slows down again at very high acid concentrations because of the formation of large amounts of XVI.



XXVII



XXVIII

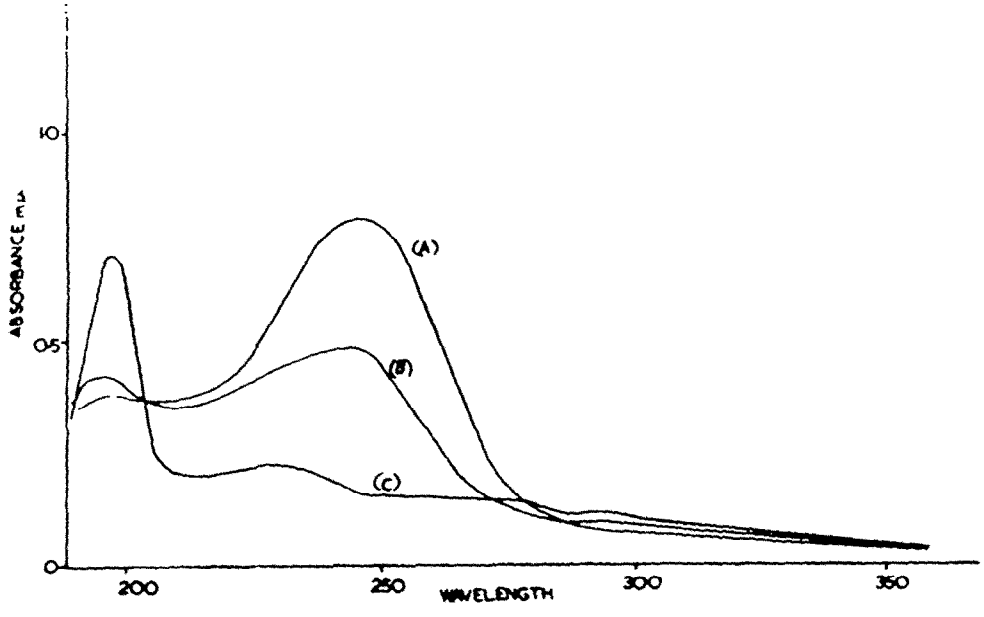


FIG. 5. UV spectra of piperidine adduct ($3{\cdot}88 \times 10^{-4}$M) in 0·2N H_2SO_4–EtOH (2:1 by volume) after (A) 15 min; (B) 113 min; (C) 6 days.

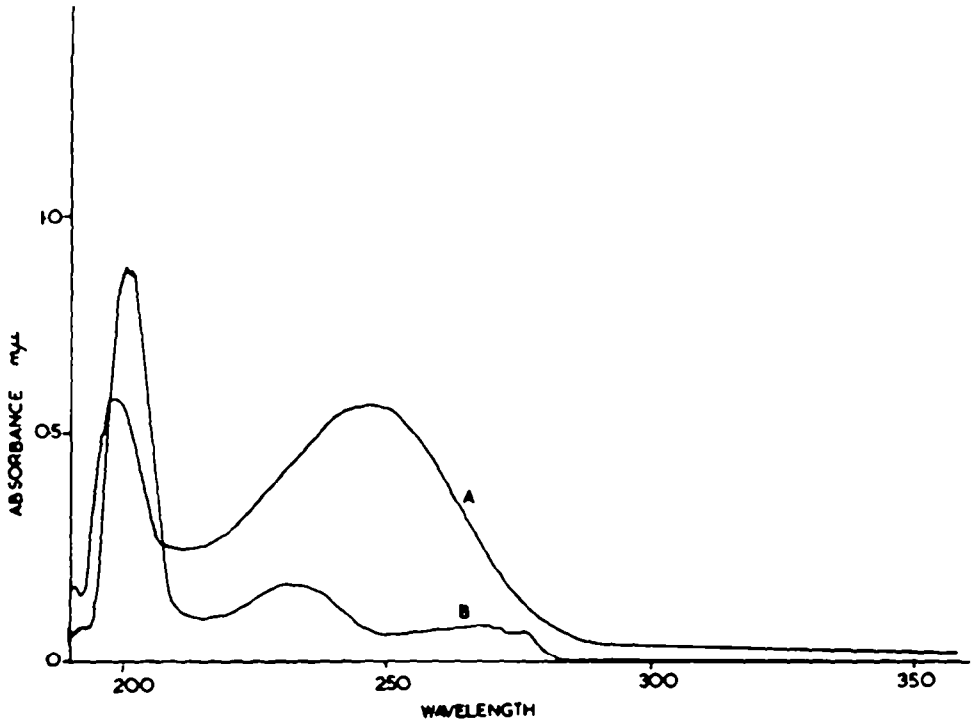


FIG. 6. UV spectra of piperidine adduct ($4{\cdot}3 \times 10^{-5}$M) in 2N H_2SO_4 after (A) 50 min; (B) 14 hr.

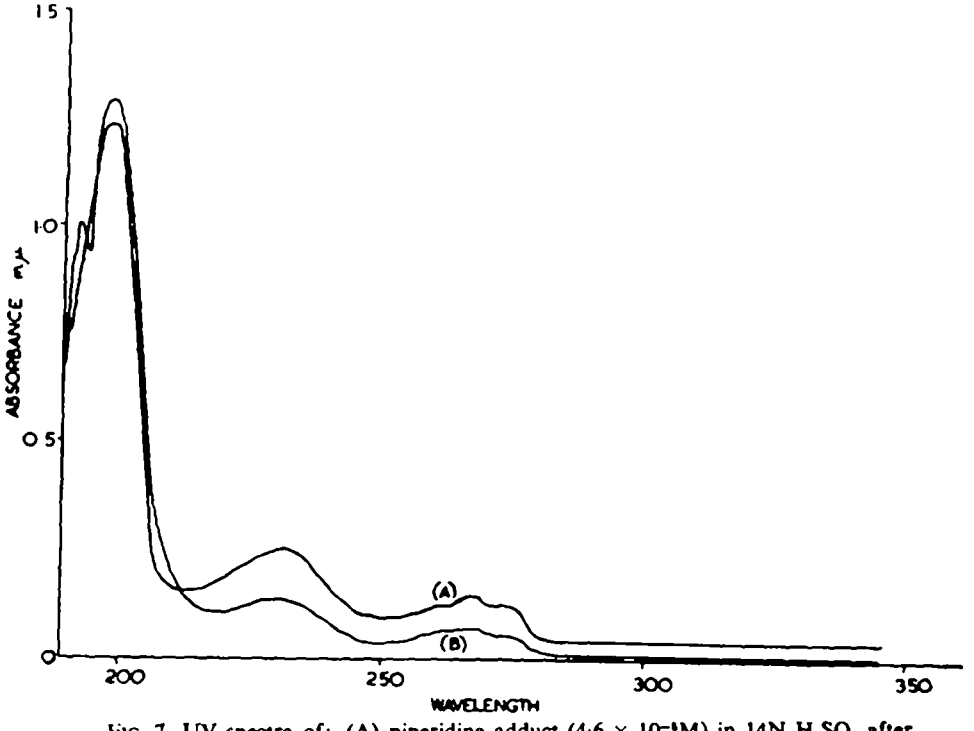


FIG. 7. UV spectra of: (A) piperidine adduct ($4{\cdot}6 \times 10^{-5}$M) in 14N H_2SO_4 after 30 min; (B) 2,3-dihydroisoxazalo[2.3-a]-pyridinium perchlorate ($2{\cdot}91 \times 10^{-5}$M) in water.

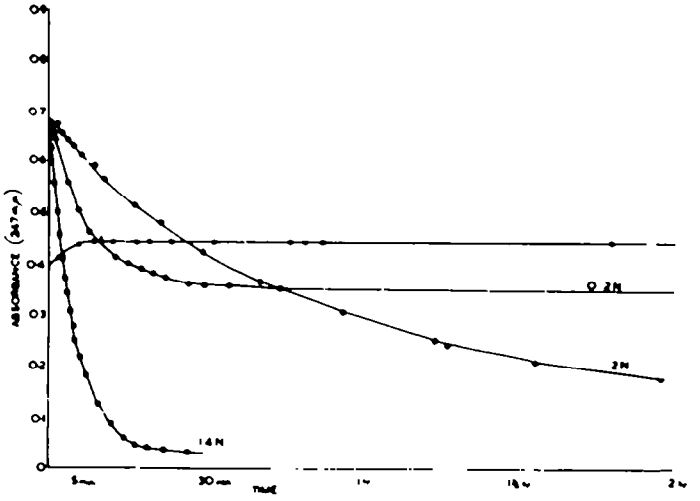


FIG. 8. Decrease of absorbance at 247 mμ with time for piperidine adduct in: ⊡⊡⊡ 14N H_2SO_4–EtOH (2:1); ○○○ 2N H_2SO_4–EtOH (2:1); . . . 0·2N H_2SO_4–EtOH (2:1); × × × 0·01M acetate buffer pH 4·9–EtOH (2:1).

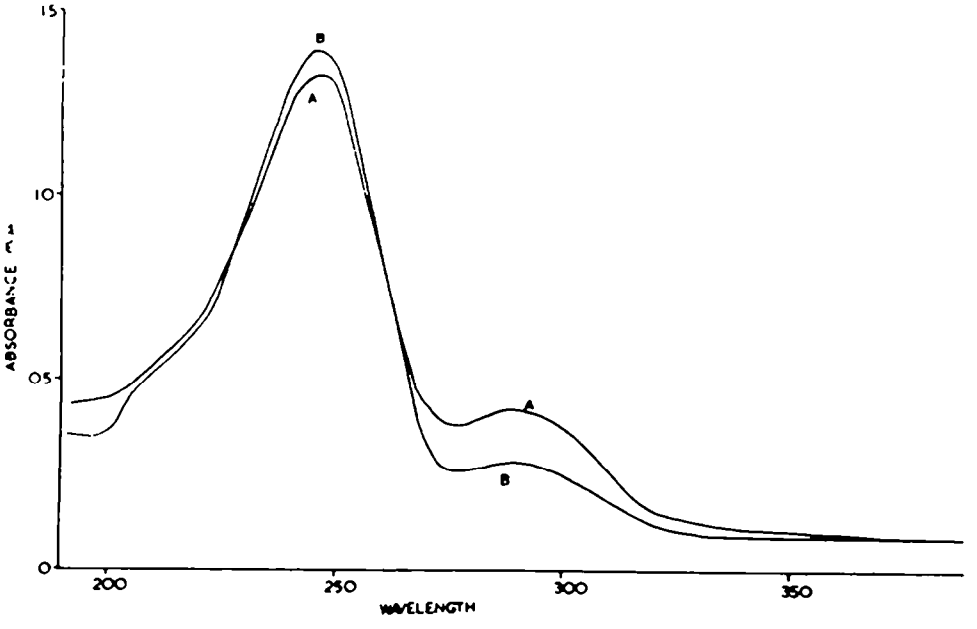
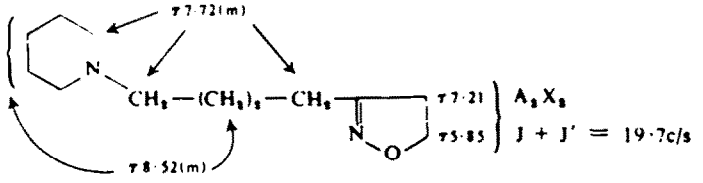


FIG. 9. UV spectra of piperidine adduct ($1·03 \times 10^{-4}$M) in 0·01M acetate buffer–EtOH (2:1) after (A) 90 sec; (B) 11 min.

Hydrogenation of the adducts. Boekelheide and Feely[1] hydrogenated the piperidine adduct III in ethyl acetate over Adams catalyst, found an uptake of four molecules of hydrogen, and isolated a product $(C_7H_{15}NO)_x$ b.p. 130°/1 mm, which was not identified. In our hands, the hydrogenation product under these conditions was a complex mixture. The lower boiling fraction was shown to be essentially homogeneous by TLC and yielded a crystalline (−)-di-O-(*p*-toluoyl)-D-tartrate (diptolate), and a dibenzoyl derivative. The NMR spectra of the crude base (10%, benzene) showed that the piperidine ring had been removed by hydrogenolysis, and that the isoxazoline ring had been reduced and opened. Multiplets at τ 6·15 (2H) and τ 7·8 (1H) were observed together with a singlet τ 7·35 (3H) and a complex multiplet at τ 8·4–9·3. [In tetrachloroethylene (20% soln) the corresponding peaks were at τ 6·34 (2H), τ 7·18 (1H), τ 6·70 (3H) and τ 8·1–9·3].

This pattern is believed to arise from the structure XXVIII, 3-aminoheptan-1-ol, in which the 3H singlet at τ 7·35 results from the rapid exchange of the amino and hydroxyl protons. This is supported by the disappearance of the τ 7·35 peak on deuteration and on formation of the diptolate, and by the observation of similar behaviour in 3-aminopropan-1-ol, which shows (25%, $CHCl_3$) a triplet (2H) at τ 6·3, a quintet (2H) at τ 8·33 and a triplet (2H) at τ 7·12 on which is superimposed the singlet (3H), τ 7·18, which disappears in D_2O.

The higher boiling fraction of the hydrogenation mixture was shown by TLC to contain at least four components, two present in major amounts. One of the major components could be isolated by chromatography on silica gel, and was characterized as the picrate and diptolate. Analysis of these derivatives indicated that the corresponding base had the structure XXIX, and this was supported by the NMR spectra of the base, as indicated.



XXIX

EXPERIMENTAL

M.ps are uncorrected. IR spectra were measured as smears (liquids) or Nujol mulls (solids) using a Perkin-Elmer 237 spectrometer. UV spectra were recorded with a Perkin-Elmer 137 UV spectrophotometer. Proton chemical shifts are expressed in τ units and were measured with a Perkin-Elmer 40 Mc/s instrument or a Perkin-Elmer R10 (60 Mc/s) instrument as indicated. TMS, tetramethylammonium sulphate (TMAS) or β-trimethylsilyl propionic acid sodium salt (TMPSA) were used as internal references.

2,3-*Dihydroisoxalo*[2.3-a]*pyridinium bromide* (I)

This was prepared as previously described.[1] It had m.p. 149–150°, from EtOH (lit. 152–155°). The compound was shown to be pure by TLC (MeOH-kieselgel G).

The *perchlorate* had m.p. 159–160° from EtOH. (Found: C, 37·8; H, 4·2; N, 6·6. $C_7H_8ClNO_5$ requires: C, 37·9; H, 3·7; N, 6·3%.)

3-(4-*Piperidin*-1′-*yl*-1,3-*butadienyl*)2-*isoxazoline* (VII)

Preparation of this compound[1] was found to give low and variable yields (10–41%), so the following procedure was adopted. The bromide I (52 g) and piperidine (250 ml) were heated on a boiling water-bath with occasional shaking for 1 hr. The mixture was allowed to cool slowly and kept at 0° overnight. Dilution with ice–water (500 ml), followed by cooling in ice–salt gave 30·9 g (58%) of the adduct VII, m.p. 120–121°. Dilution to 1 l. and keeping at 0° gave a small further amount (1·85 g, 3·5%), m.p. 119–121°. Repeated crystallization from EtOH to constant m.p. gave material m.p. 121–122° (lit.[1] 124–126°).

3-(4-*Dimethylamino*-1,3-*butadienyl*)2-isoxazoline (VI)

This was prepared by heating I (8·0 g) and 25% aqueous dimethylamine soln (175 ml) for a short time on the water bath. The mixture was allowed to stand overnight, then cooled in ice–salt and treated as described for the piperidino compound to give, after crystallization from AcOEt and EtOH, 653 mg of the *dimethylamine adduct*, m.p. 120–121°. (Found: C, 64·7; H, 8·6; N, 16·7. $C_9H_{14}N_2O$ requires: C, 65·0; H, 8·5; N, 16·9%.)

Acid degradation of adduct (VII)

(a) *UV studies.* (i) A weighed quantity of the adduct (ca. 0·015 mmol) was dissolved in the appropriate acid (20 ml), the soln diluted rapidly with the acid (1:20) and the UV spectrum taken at intervals.

(ii) A soln of the adduct (1 ml, ca. 1×10^{-4} M) in 95% benzene-free EtOH was added to the appropriate acid or buffer soln (2 ml), mixed rapidly, and the spectrum observed at intervals.

(b) *Reaction in hydrobromic acid.* A solution of the adduct VII (1 g) in HBr (10 ml, 50% w/w) and water (10 ml) was allowed to stand at room temp for 4 days. The mixture was evaporated to dryness under reduced press, the residue re-evaporated with water (3 × 100 ml), dissolved in water (100 ml) and decolorized with charcoal. The soln was treated with Amberlite IR-4*b* resin (OH^- form; 2 g) and the soln and washings evaporated to give a syrup which slowly crystallized (1·6 g). Recrystallization from acetonitrile gave piperidine hydrobromide (0·33 g, 41%) m.p. 232–234°, which after repeated crystallization from MeOH–ether and isopropanol had m.p. 235–236° (lit.[15] 235°), and was identical (mixed m.p. and IR spectrum) with an authentic sample.

The filtrate from the acetonitrile crystallization gave with ether 1·06 g of a mixture (as evidenced by TLC and NMR) of approximately equal parts of piperidine hydrobromide and I. This mixture in water (5 ml) was treated with an equal volume of sat $NaClO_4$ aq, the soln cooled to 0° and further $NaClO_4$ added to precipitate the perchlorate of I (0·37 g, 35%), which after repeated crystallization from EtOH had m.p. 159–160° and was identical (mixed m.p. and IR spectrum) with an authentic sample.

Hydrogenation of adduct (VII)

The adduct (10 g) in purified (acid-free) AcOEt (120 ml) was hydrogenated with PtO_2 catalyst (1 g) at 25° and 60 lbs/in² until uptake of H had ceased (94% uptake for $4H_2$). Evaporation of the filtered reaction mixture gave a syrup (9·1 g) which on distillation gave a fraction (A), b.p. 72°/0·3 mm (0·62 g), a fraction (B), b.p. 118–128°/0·3 mm (2·05 g), and much higher boiling material (b.p. 128–230°/0·3 mm) (2·7 g) and a non-distillable residue.

Fraction (A) contained substantially one component (by TLC) and on reaction with (-)-di-(O-*p*-toluoyl)-D-tartaric acid[16] in ether, followed by crystallization from EtOH, gave 3-*aminoheptan*-1-*ol*(−)-*di*-O-(p-*toluoyl*)-D-*tartrate*, m.p. 195–196°. (Found: C, 62·4; H, 6·8; N, 2·71. $C_{37}H_{44}NO_8$ requires: C, 62·6; H, 6·8; N, 2·71%.)

Reaction with BzCl–NaOH followed by chromatography on silica gel and crystallization from cyclohexane gave the N,O-*dibenzoyl deriv* of 3-aminoheptan-1-ol, m.p. 97–99°. (Found: C, 73·85; H, 8·0; N, 4·07. $C_{21}H_{25}NO_3$ requires: C, 74·3; H, 7·45; N, 4·13%.)

The fraction (B) by TLC on Kieselgel G–methanolic ammonia showed 4 components (2 major and

[15] C. A. Bischoff, *Ber. Dtsch. Chem. Ges.* **31**, 2839 (1898).
[16] D. A. A. Kidd, *J. Chem. Soc.* 4675 (1961).

2 minor). Chromatography (1·85 g) on silica gel furnished on elution with 1% methanolic ammonia, a fraction (0·52 g) consisting of one of the major components contaminated with a small amount of a minor component. This fraction gave 3-(4-*piperidine*-1-*yl butyl*)2-*isoxazoline picrate*, m.p. 141·5–142·5°, from EtOH. (Found: C, 49·4; H, 5·7; N, 15·9. $C_{18}H_{23}N_5O_8$ requires: C, 49·2; H, 5·75; N, 15·9%) and the corresponding (−)-*di*-O-(p-*toluoyl*)-D-*tartrate*, m.p. 130–131° from AcOEt. (Found: C, 64·2; H, 6·7; N, 4·37. $C_{33}H_{44}N_2O_8$ requires: C, 64·4; H, 6·8; N, 4·7%.)

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