802. *Quinolizines. Part IV.*[1] *The Synthesis of* 1-*Amino-quinolizinium Salts.*

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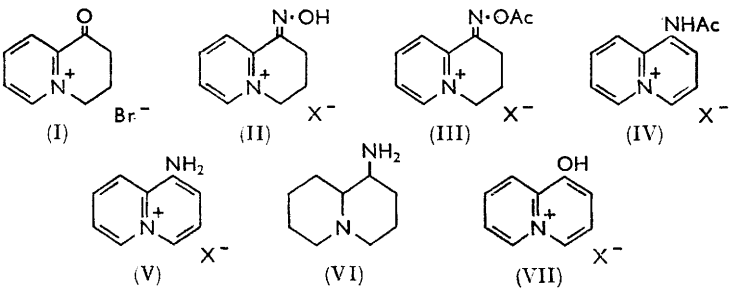
Aromatisation of the oxime (II) by hot acetic anhydride in the presence of hydrogen chloride or of sulphuric acid gives 1-acetamidoquinolizinium salts (IV), hydrolysed by hot mineral acid to 1-aminoquinolizinium salts (V). The properties of the 1-amino-compounds (V) are reported.

We have previously described [1,2] the synthesis of alkyl- and of aryl-quinolizinium salts, and a number of other methods are available for the preparation of such compounds.[3] The only simple quinolizinium compounds containing potentially reactive substituents which have been reported are the 4-quinolizone,[4a] some hydroxy-[4b] and methoxycarbonyl-4-quinolizones,[4a,c] and the various polycarboxylic acids described by Diels, Alder *et al.*[4d]

[1] Part III, Glover and Jones, *J.*, 1959, 1686.
[2] Glover and Jones, *J.*, 1958, 3021.
[3] Boekelheide and Gall, *J. Amer. Chem. Soc.*, 1954, **76**, 1832; Richards and Stevens, *J.*, 1958, 3067; Nesmeyanov and Rybinskaia, *Doklady Akad. Nauk S.S.S.R.*, 1957, **116**, 93.
[4] (*a*) Boekelheide and Lodge, *J. Amer. Chem. Soc.*, 1951, **73**, 3681; (*b*) Adams and Reifschneider, *ibid.*, 1959, **81**, 2537; (*c*) Bohlmann, Ottawa, and Keller, *Annalen*, 1954, **587**, 162; (*d*) Diels, Alder, Friedrichsen, Klare, Winkler, and Schrum, *ibid.*, 1933, **505**, 103.

As part of a general study of simple quinolizinium compounds we have synthesised 1-aminoquinolizinium salts (V) and report below the synthesis and some of the properties of this amine.

The ketone bromide [5] (I) with hydroxylamine in hot absolute ethanol gave a colourless crystalline solid of sharp and reproducible melting point. Analytical figures for this material were, however, intermediate between those expected for the oxime chloride (II; X = Cl) and the oxime bromide (II; X = Br) and it was assumed to be a mixed crystal. This was confirmed by its conversion into the pure chloride (II; X = Cl) or pure bromide (II; X = Br) by passage through anion-exchange columns, and when all three materials were converted into the same picrate (II; X = picrate). Another such mixed crystal has been observed in this work [compound (IV)].



It has been reported [6a b] that α-tetralone oxime is converted by acetic anhydride into the *O*-acetyl oxime, which undergoes Wolff aromatisation when heated with dry hydrogen chloride in a mixture of acetic acid and anhydride: the products are α-naphthylamine hydrochloride and *N*-acetyl-α-naphthylamine, the yield of acetyl derivative being greater as larger proportions of acetic anhydride are used. Similar reactions with the oxime (II) should give 1-aminoquinolizinium derivatives. Hot acetic anhydride gave the expected *O*-acetyl derivative (III; X = Br) but its isolation and purification were difficult and the yield was low. The *O*-acetyl oxime bromide (III; X = Br) was converted into the chloride (III; X = Cl) by anionic exchange and this was heated in solution in acetic anhydride while a stream of dry hydrogen chloride was passed through the solution. The product was 1-acetamidoquinolizinium chloride (IV; X = Cl); the evidence for this formulation is presented below. The over-all yield was much better if the oxime bromide (II; X = Br) was boiled for 4 hr. with acetic anhydride containing a drop of sulphuric acid; isolation of the *O*-acetyl oxime (III) was then unnecessary.

Catalytic hydrogenation of 1-acetamidoquinolizinium bromide (IV; X = Br) gave an oily decahydro-base which failed to give a crystalline derivative but showed infrared absorption at 1690 cm.$^{-1}$ (amide-CO). The base was hydrolysed by hot concentrated hydrochloric acid to 1-aminoquinolizidine (VI), characterized as its dipicrate. The same dipicrate was obtained after hydrogenation of the oxime (II), again with absorption of five mol. of hydrogen. Hydrolysis of 1-acetamidoquinolizinium bromide (IV; X = Br) with hot concentrated hydrobromic acid gave 1-aminoquinolizinium hydrobromide (V; X = Br, as hydrobromide) but this proved too unstable for analysis. The amine gave a monopicrate (V; X = picrate) which was converted into a monoperchlorate (V; X = ClO_4) by anion-exchange; the instability of the hydrobromide and the formation of such mono-acid salts indicates the low basicity of the amino-group in the 1-position of the quinolizinium nucleus. This was confirmed by determination of the ultraviolet absorption of the amine (V) over a range of pH values. Practically no change in the spectrum was noticeable

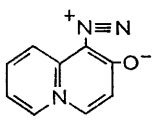
[5] Glover and Jones, *J.*, 1958, 1750.

[6] (*a*) Schroeter, Gotsky, Huang, Irmisch, Laves, Schrader, and Stier, *Ber.*, 1930, **63**, 1308; (*b*) Voroshtzov and Koptyug, *Khim. Nauka i Prom.*, 1957, **2**, 657.

from pH 10 to pH 1, the major long-wave maximum being at 3610 Å. In 2N-sulphuric acid the appearance of a new maximum at 3280 Å was noted although the 3610 Å maximum was still present with reduced intensity, and in 50% sulphuric acid only the 3280 Å maximum was present. This change in absorption must be associated with protonation of the 1-amino-group (cf. α-naphthylamine [7] where the long-wave maximum is at 3073 Å and α-naphthylamine hydrochloride where it is at 2732 Å). From these observations the 1-aminoquinolizinium salts are certainly less basic on the 1-amino-group than *p*-nitroaniline (pK_b of 1·2 [8]) and are probably as weak as 2,4-dinitroaniline. 1-Aminoquinolizinium perchlorate (V; X = ClO_4) with boiling acetic anhydride gave a moderate yield of a 1-acetamidoquinolizinium salt, isolated as the picrate (IV; X = picrate); attempts to acetylate the amine under milder conditions were unsuccessful.

The reaction between the 1-aminoquinolizinium chloride (V; X = Cl) and nitrous acid was studied under various conditions. Treatment of the amine chloride in very dilute acid solution with cold aqueous sodium nitrite gave a neutral compound (A), $C_9H_7N_3O$; its structure is discussed below. Treatment of the chloride in concentrated hydrochloric or hydrobromic acids with sodium nitrite gave no diazonium compound (no colour with alkaline β-naphthol), and no 1-hydroxyquinolizinium salt could be isolated. Treating a solution of the chloride (V; X = Cl) in acetic–sulphuric acid with nitrosylsulphuric acid gave a diazonium compound (the solution gave a deep red colour with alkaline β-naphthol) but no 1-hydroxyquinolizinium salt could be isolated. Finally, diazotisation of the 1-aminoquinolizinium chloride hydrochloride (V; X = Cl, as hydrochloride) was achieved by the use of pentyl nitrite in ethanol; 1-hydroxyquinolizinium picrate (VII) was isolated after the mixture had been diluted and heated. The picrate (VII) showed no depression in a mixed melting point with a sample obtained [9] by dehydrogenation of the ketone (I).

The compound (A), $C_9H_7N_3O$, must be substituted in the 2-position of the quinolizinium nucleus, as it is a neutral molecule and not a salt. Formulation as a diazo-oxide (*e.g.*, VIII) is thus ruled out since all such structures carry a formal positive charge (also the diazo-oxides are highly coloured, whereas compound A is colourless). The most likely structure is of the furazan type (IX), presumably formed by nitrosation of the 1-aminoquinolizinium salt at position 2, with subsequent oxidative cyclisation. Hydrogenation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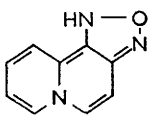
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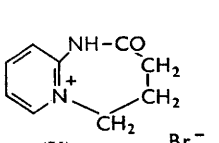
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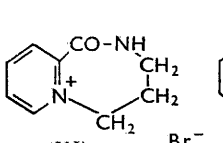
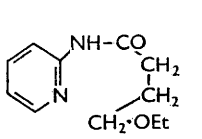

(XI)


(XII)

of compound (A) led to the absorption of 2 mol. of hydrogen only, but no pure product was obtained. Compound (A) was very unstable to acids but no products of this reaction could be isolated; the crude product after acid hydrolysis gave no ferric chloride colour and no crystalline picrate, and failed to give a copper complex. Furazans are reported [10] to give isoxazoles on treatment with acid but the yields are mostly poor and mixtures are usually obtained. The difficulty of obtaining compound (A) in quantity has precluded a more detailed study.

During the first experiments with the acetic anhydride–sulphuric acid and the oxime (II; X = Br), a compound (B) crystallised from the solution on cooling, and was found to be an isomer of the oxime. It was assumed to be the product of Beckmann rearrangement and it is therefore (X) or (XI); an attempt to synthesise the lactam (X) by cyclisation of the amide (XII) failed, the amide link being hydrolysed.

[7] Rollett, *Monatsh.*, 1937, **70**, 425.
[8] Farmer and Warth, *J.*, 1904, **85**, 1726.
[9] Glover, Ph.D. Thesis, Keele, 1959.
[10] Cusmano and Giambrone, *Gazzetta*, 1951, **81**, 499.

Experimental

M. p.s were determined on a Kofler block.

1,2,3,4-*Tetrahydro*-1-*hydroxyiminoquinolizium Salts* (II).—Hot solutions of sodium acetate (3 g.) and hydroxylamine hydrochloride (3 g.) in absolute ethanol were mixed, cooled, and filtered from sodium chloride. The filtrate was boiled with the ketone bromide (I) (3 g.) for 0·5 hr. Concentration, followed by cooling, gave crystals which from absolute ethanol formed prisms, m. p. 254° (2·8 g.) (Found: C, 47·6; H, 5·3. Calc. for $C_9H_{11}BrN_2O$: C, 44·5; H, 4·6. Calc. for $C_9H_{11}ClN_2O$: C, 54·4; H, 5·6%). A solution of this material in 95% ethanol was percolated through a chloride-loaded column of Amberlite IRA-400, giving the *oxime chloride* (II; X = Cl), crystallising from absolute ethanol as prisms, m. p. 260° (Found: C, 54·3; H, 5·6%). Percolation through a bromide-loaded column gave the *oxime bromide* (II; X = Br), prisms (from absolute ethanol), m. p. 258° (Found: C, 44·6; H, 4·5%), $\lambda_{max.}$ 2460, 2970 Å ($\log_{10}\varepsilon$ 3·86, 4·13 in H_2O). Aqueous solutions of all three oxime salts gave, with aqueous sodium picrate, the *picrate* (II; X = picrate), recrystallising from 95% ethanol as orange-brown prisms, m. p. 247—249° (Found: C, 46·0; H, 3·4. $C_{15}H_{13}N_5O_8$ requires C, 46·1; H, 3·35%).

1-*Acetoxyimino*-1,2,3,4-*tetrahydroquinolizinium Bromide* (III; X = Br).—The oxime bromide (II; X = Br) (0·48 g.) in acetic anhydride (50 ml.) was boiled for 4 hr. The anhydride was removed under reduced pressure, and the residue was twice evaporated to dryness under reduced pressure with 10 ml. portions of absolute ethanol. The residue was dissolved in absolute ethanol, treated with charcoal, filtered, and then treated with ethyl acetate. The precipitated *O-acetyl oxime bromide* (III; X = Br) recrystallised from ethanol–ethyl acetate as prisms, m. p. 228° (0·24 g., 43%) (Found: C, 46·3; H, 4·8. $C_{11}H_{13}BrN_2O_2$ requires C, 46·5; H, 4·6%), $\lambda_{max.}$ 2620, 3310 Å ($\log_{10}\varepsilon$ 3·73, 3·92 in H_2O).

1-*Acetamidoquinolizinium Salts* (IV).—(*a*) A slow stream of dry hydrogen chloride was passed through a solution of the *O*-acetyl oxime bromide (III; X = Br) (1·4 g.) in acetic acid (9 ml.) and acetic anhydride (72 ml.) at 95° for 2·5 hr. The solvents were removed under reduced pressure, and the residue was percolated in 95% ethanol through a chloride-loaded Amberlite IRA-400 column, giving 1-*acetamidoquinolizinium chloride* (IV; X = Cl), recrystallising from absolute ethanol (charcoal) as prisms m. p. 292° (0·20 g., 18%) (Found: C, 59·2; H, 5·0. $C_{11}H_{11}ClN_2O$ requires C, 59·3; H, 5·0%), $\lambda_{max.}$ 3280 Å ($\log_{10}\varepsilon$ 4·04 in H_2O). The *picrate* (IV; X = picrate) crystallised from 95% ethanol as orange-brown prisms, m. p. 194° (Found: C, 49·3; H, 3·5. $C_{17}H_{13}N_5O_8$ requires C, 49·2; H, 3·1%).

(*b*) The oxime bromide (II; X = Br) (1 g.) in acetic anhydride (110 ml.) and concentrated sulphuric acid (5 drops) was boiled for 4 hr. Evaporation under reduced pressure and treatment of the residue with absolute ethanol and ethyl acetate gave 1-*acetamidoquinolizinium bromide* (IV; X = Br), prisms (from absolute ethanol), m. p. 269° (0·47 g., 43%) (Found: C, 49·75; H, 4·0; N, 10·65. $C_{11}H_{11}BrN_2O$ requires C, 49·45; H, 4·15; N, 10·5%), $\lambda_{max.}$ 3280 Å ($\log_{10}\varepsilon$ 3·99 in H_2O). The chloride and the bromide gave the same picrate, m. p. 194°.

(*c*) The oxime bromide (II; X = Br) (0·5 g.) in acetic anhydride (55 ml.) containing 2 drops of concentrated sulphuric acid was boiled for 1 hr., then cooled. A small quantity of solid was obtained: it recrystallised from 95% ethanol, to give the bicyclic *amide* (X or XI), m. p. 204° (Found: C, 44·5; H, 4·1; N, 11·85. $C_9H_{11}N_2OBr$ requires C, 44·6; H, 4·5; N, 11·5%), $\lambda_{max.}$ 2370, 2900 Å (in 95% EtOH).

1-*Aminoquinolizidine* (VI).—(*a*) 1-Acetamidoquinolizinium chloride (IV; X = Cl) (0·113 g.) in glacial acetic acid (25 ml.) was hydrogenated to completion over Adams platinum oxide at 752 mm. and 18° (uptake 60·92 ml. ($5H_2$; 61·81 ml.). The solution was filtered, then evaporated to dryness, and the residue was boiled with concentrated hydrochloric acid for 1 hr. Evaporation of the acid solution gave the amine dihydrochloride, which was converted into 1-*aminoquinolizidine dipicrate*, golden prisms (from methanol), m. p. 244° (Found: C, 41·5; H, 3·8. $C_{21}H_{24}N_8O_{14}$ requires C, 41·2; H, 3·95%).

(*b*) A solution of 1,2,3,4-tetrahydro-1-hydroxyiminoquinolizinium bromide (II; X = Br) (0·228 g.) in 95% ethanol (30 ml.) was hydrogenated to completion over Adams platinum oxide at 764·3 mm. and 18° (uptake 106·1 ml.; $5H_2$; 105·0 ml.). Filtration and evaporation gave a residue from which a picrate was prepared, having m. p. 240° not depressed on admixture with the picrate prepared by method (*a*).

1-Aminoquinolizinium Salts (V).—1-Acetamidoquinolizinium bromide (IV; X = Br) (0·2 g.) in 48% hydrobromic acid (25 ml.) was boiled for 2 hr. The acid was removed under reduced pressure, the residue dissolved successively in water and in ethanol, the solvent being removed in each case under reduced pressure, and finally crystallised from absolute ethanol–ethyl acetate, giving the amine bromide hydrobromide as prisms, melting with decomposition between 240° and 248°. Samples for analysis were dried for 8 hr. at 20°/0·5 mm. since the salt decomposed at higher temperatures (Found: C, 36·2; H, 3·5; N, 9·0; Br, 51·1. Calc. for $C_9H_{10}Br_2N_2$: C, 35·25; H, 3·3; N, 9·2; Br, 52·2%). This salt had $\lambda_{max.}$ 2560, 3610 Å ($\log_{10}$ ε 3·85, 3·93 in H_2O), $\lambda_{max.}$ 2780, 2850, 3280 Å ($\log_{10}$ ε 3·57, 3·57, 4·20 in 50% H_2SO_4). The *picrate* (V; X = picrate) crystallised from 95% ethanol as orange-brown prisms, m. p. 204° (Found: C, 48·4; H, 2·7. $C_{15}H_{11}N_5O_7$ requires C, 48·3; H, 3·0%). The *perchlorate* (V; X = ClO_4), prepared from the picrate by anionic exchange, crystallised from absolute ethanol as pale yellow rhombs, m. p. 283° (Found: C, 44·8; H, 4·0; N, 11·3. $C_9H_9ClN_2O_4$ requires C, 44·2; H, 3·7; N, 11·5%), $\lambda_{max.}$ 3620 Å ($\log_{10}$ ε 3·94 in H_2O).

Acetylation of 1-Aminoquinolizinium Perchlorate.—A solution of the perchlorate (V; X = ClO_4) (0·25 g.) in acetic anhydride (25 ml.) was boiled for 1 hr. Removal of the solvent, dilution with water, and further evaporation gave a sticky solid, converted into 1-acetamidoquinolizinium picrate, m. p. and mixed m. p. 194°. Acetic anhydride and aqueous sodium acetate at room temperature did not effect acetylation.

Reaction between 1-Aminoquinolizinium Salts and Nitrous Acid.—In all experiments the 1-acetamidoquinolizinium chloride (IV; X = Cl) was hydrolysed by hot concentrated hydrochloric acid for 1 hr.; the acid was removed under reduced pressure, and the residual hydrochloride was freed from excess of acid by evaporation with ethanol.

(*a*) The crude hydrochloride [from 0·396 g. of the amide (II; X = Cl)] was dissolved in 2N-hydrochloric acid (3 ml.) at −8° and treated with an excess of aqueous sodium nitrite. A solid precipitate was formed, which crystallised from water as flakes, m. p. 180° (0·263 g., 85%) (Found: C, 61·9; H, 3·7; N, 24·8. $C_9H_7N_3O$ requires C, 62·3; H, 4·1; N, 24·3%), $\lambda_{max.}$ 3450 Å ($\log_{10}$ ε 4·25 in H_2O). The *substance* is very soluble in acetone; soluble in hot ethanol, benzene, and water, but almost insoluble in the cold, and insoluble in ether; it gives it gives no colour with ferric chloride and no picrate.

(*b*) To a solution of the crude hydrochloride (0·16 g.) in 95% ethanol containing one drop of concentrated hydrochloric acid at 0° was added a slight excess of pentyl nitrite. A few drops of the resulting solution, added to alkaline β-naphthol, gave a deep red colour and a purple precipitate. The bulk of the ethanol was removed, 5N-hydrochloric acid (10 ml.) was added, and the mixture heated for 1 hr., after which the acid was removed under reduced pressure. A sample of the aqueous solution from the residual solid gave an intense green colour with neutral ferric chloride solution; *1-hydroxyquinolizinium picrate* was obtained by treatment of the aqueous solution with aqueous sodium picrate and crystallised from water as orange prisms, m. p. 210—214° (decomp.) (Found: C, 47·2; H, 2·7; N, 15·25. $C_{15}H_{10}N_4O_8$ requires C, 48·0; H, 2·95; N, 14·9%). A mixed m. p. with 1-hydroxyquinolizinium picrate obtained [9] by dehydrogenation of the ketone (I) showed no depression.

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