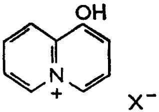
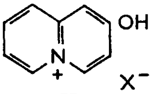
529. *Quinolizines. Part VI.* The Synthesis and Properties of 2-Quinolizone.*

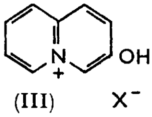
By A. Fozard and Gurnos Jones.

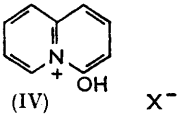
2-Hydroxyquinolizinium bromide (II) has been prepared by the action of silver acetate on 2-bromoquinolizinium bromide (VII), and converted by alkali into 2-quinolizone (VI). The properties of the 2-hydroxyquinolizinium salts and of 2-quinolizone are reported.

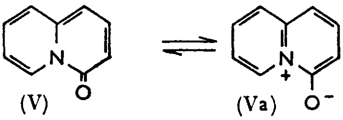
Of the four possible hydroxyquinolizinium salts (I), (II), (III), and (IV) all but the 2-hydroxyquinolizinium salts (II) have been prepared. The 1-hydroxyquinolizinium salts (I) are typically phenolic,[1] and the 3-hydroxyquinolizinium salts [2] (III) would be expected to behave similarly. The 4-hydroxyquinolizinium salts [3] (IV) are hygroscopic and can be readily converted by alkali into 4-quinolizone (V) which has properties resembling those of carbostyril [3,4] though possibly with more contribution from the dipolar structure (Va). We report below the synthesis of 2-hydroxyquinolizinium salts (II) and their conversion into 2-quinolizone (VI or VIa).

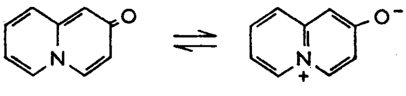

(I)


(II)


(III)


(IV)


(V) (Va)


(VI) (VIa)

2-Hydroxyquinolizinium bromide (II; X = Br) was obtained in high yield from 2-bromoquinolizinium bromide [1] (VII) by treatment with silver acetate in hot acetic acid. The rate of conversion was slow (90% conversion after 40 hours), which is surprising in view of the positive charge carried by the ring system. Treatment of 2-hydroxyquinolizinium bromide (II; X = Br) with saturated aqueous sodium carbonate gave the chloroform-soluble 2-quinolizone (VI), purified by repeated sublimation. The quinolizone (VI) was very hygroscopic and was soluble both in water and in organic solvents.

The infrared (i.r.) spectrum of 2-hydroxyquinolizinium bromide (II; X = Br), showed medium strength absorption bands at 3250 cm.$^{-1}$ (hydrogen-bonded OH) and at 1650 cm.$^{-1}$ (cyclic amide CO), while the free 2-quinolizone (VI) showed a strong band at 1634 cm.$^{-1}$. The reported [3] position for the carbonyl stretching absorption in 4-quinolizone (V) is 6·0 μ (1666 cm.$^{-1}$) and the shift to longer wavelength shown by 2-quinolizone is in accord with the observations by Katritzky and Jones [5] on the carbonyl stretching frequency of 2- and 4-pyridones (2-pyridones absorb at 1655—1665 cm.$^{-1}$ and 4-pyridones at 1575 cm.$^{-1}$ with a second strong band due to the pyridone ring C=C, C=N stretching at 1623—1640 cm.$^{-1}$). The ultraviolet (u.v.) absorption maxima were determined over a range of pH values and the pK_a calculated to be approximately 4, which indicates that the 2-hydroxyquinolizinium salts are fairly strong acids.

The reduction of 2-quinolizone (VI) proceeded rapidly, but under the conditions used

---

* Part V, *J.*, 1963, 2203.

[1] Fozard and Jones, *J.*, 1963, 2203.

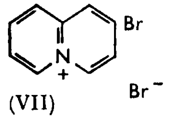
[2] Schraufstätter, *Angew. Chem.*, 1962, **74**, 874.

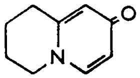
[3] Boekelheide and Lodge, *J. Amer. Chem. Soc.*, 1951, **73**, 3681.

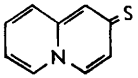
[4] Boekelheide and Gall, *J. Org. Chem.*, 1954, **19**, 499.

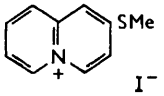
[5] Katritzky and Jones, *J.*, 1960, 2947.

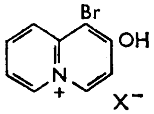
by Boekelheide and Lodge[3] gave only a tetrahydro-derivative. This compound (VIII) showed the expected strong absorption peaks in the i.r. region at 1642 and 1550 cm.$^{-1}$ characteristic of a 4-pyridone[5] and a u.v. spectral maximum at 2600 shifting to 2390 Å on acidification (1-methyl-4-pyridone absorbs at 2600 in neutral and 2370 Å in acid solution).[6] Treatment of 2-quinolizone (VI) with phosphorus pentasulphide gave a compound which was not obtained pure, but which after sublimation showed the expected i.r. maximum at 1090 cm.$^{-1}$ characteristic of the C=S grouping.[5,7] The quinolizinethione (IX) when treated with methyl iodide gave the methylthioquinolizinium iodide (X; X = I) which showed the u.v. maxima characteristic of simple quinolizinium salts.[8] In another reaction of the " pyridone " type 2-quinolizone (VI) was heated with phosphorus tribromide to give 2-bromoquinolizinium bromide (VII).


(VII)


(VIII)


(IX)


(X)


(XI)

No account has been given of substitutions performed on 4-quinolizone (V) other than those in which the oxygen function is replaced. In view of the ready electrophilic substitution of 1-hydroxyquinolizinium salts (I),[1] the reaction between 2-hydroxyquinolizinium bromide (II; X = Br) and bromine in hydrobromic acid was examined. The product was 1-bromo-2-hydroxyquinolizinium bromide (XI; X = Br) obtained also by an alternative route (Part VII, following Paper). The reaction between 1-hydroxyquinolizinium salts (I) and dilute nitric acid gives a variety of nitration products,[9] but treatment of 2-hydroxyquinolizinium bromide (II; X = Br) with dilute nitric acid gave in good yield 1-bromo-2-hydroxyquinolizinium nitrate (XI; X = NO_3). Bromination in nitric acid has been reported to give high yields of 4,5-dibromo-1-*p*-bromophenylpyrazole from the 4-bromo-derivative.[10]

An attempt to introduce the cyano-group into the 1-position by heating 2-hydroxyquinolizinium bromide (II; X = Br) with dilute nitric acid containing cyanide ions gave only the nitrate (II; X = NO_3).

EXPERIMENTAL

Melting points were determined on a Kofler block apparatus. Ultraviolet absorption spectra were determined in aqueous solution unless otherwise stated. Infrared absorption spectra were determined in Nujol mulls.

2-*Hydroxyquinolizinium Bromide* (II; X = Br).—A suspension of silver acetate (3·25 g.) in glacial acetic acid (100 ml.) was added to 2-bromoquinolizinium bromide (VII) (2·50 g.) in acetic acid (50 ml.), and the mixture stirred and boiled under reflux for 40 hr. After being cooled in ice–water the mixture was filtered and the filtrate evaporated to dryness under reduced pressure. The residue was dissolved in 50% aqueous hydrobromic acid and warmed on a water-bath for 0·25 hr. The solution was then evaporated to dryness under reduced pressure, water added, and the solution again evaporated to give a solid, which was suspended in ethanol, and the mixture cooled in ice–water and filtered. More solid was obtained by addition of ethyl acetate to the filtrate. 2-*Hydroxyquinolizinium bromide hemihydrate* (as II; X = Br) (1·76 g., 90%) crystallised from ethanol–ethyl acetate as blunt needles, m. p. 258—263° (Found: C, 45·75; H, 3·7; N, 6·05. $2C_9H_8BrNO,H_2O$ requires C, 46·0; H, 3·85; N, 5·95); $\lambda_{max.}$ 2250, 2980, and 3240sh Å ($\log_{10} \varepsilon$ 4·55, 4·05, and 3·86); $\nu_{max.}$ 3250 (hydrogen bonded OH) and 1650 cm.$^{-1}$ (cyclic amide CO). The compound gave a dark red colour with aqueous

---

[6] Ross, *J.*, 1951, 1374.
[7] Spinner, *J. Org. Chem.*, 1958, **23**, 2037.
[8] Glover and Jones, *J.*, 1958, 3021.
[9] Fozard and Jones, unpublished work.
[10] Finar and Millar, *J.*, 1961, 2769.

ferric chloride. The *picrate* (II; X = picrate) was prepared by addition of aqueous sodium picrate to an aqueous solution of the hydroxyquinolizinium bromide; it formed small yellow prisms, m. p. 231°, from acetone (Found: C, 48·5; H, 2·7; N, 15·0. $C_{15}H_{10}N_4O_8$ requires C, 48·15; H, 2·7; N, 15·0%).

2-*Quinolizone* (VI).—2-Hydroxyquinolizinium bromide (II; X = Br) (4·50 g.) was treated with cold saturated aqueous potassium carbonate solution (20 ml.). Effervescence occurred and yellow oily droplets were formed. The solution was extracted several times with chloroform, the extracts were dried (Na_2SO_4), the solvent evaporated, and the residue (1·325 g., 49%) sublimed; 2-*quinolizone* formed thick yellow crystals, m. p. 127·5—129·5° (change of crystal form at 65—67°). After two more sublimations the m. p. was 128—129·5° (65—67°) (Found: N, 9·7. C_9H_7NO requires N, 9·65%); $\lambda_{max.}$ 2260, 2990, and 3250sh Å ($\log_{10} \varepsilon$ 4·50, 4·00, and 3·75); $\lambda_{max.}$ (H_2SO_4) 2160, 2870sh, 3130, and 3210 Å ($\log_{10} \varepsilon$ 4·50, 3·84, 4·07, and 4·06); $\nu_{max.}$ 1634 cm.$^{-1}$. The pK_a determined spectrophotometrically was 4 (±0·5).

6,7,8,9-*Tetrahydro*-2-*quinolizone* (VIII).—2-Quinolizone (0·35 g.) in 95% ethanol (25 ml.) was hydrogenated at atmospheric pressure, Adams platinum oxide catalyst (0·100 g.) being used. Two molar equivalents of hydrogen were quickly (0·5 hr.) absorbed, absorption then ceasing. The solution was filtered and the filtrate evaporated to dryness. The oily residue crystallised on treatment with light petroleum (b. p. 40—60°) and was filtered to give 6,7,8,9-*tetrahydro*-2-*quinolizone* (0·324 g., 93%). Sublimation gave blunt needles, m. p. 133—135° (change of crystal form 55—57°) (Found: N, 9·05. $C_9H_{11}NO$ requires N, 9·4%); $\lambda_{max.}$ 2570 Å ($\log_{10} \varepsilon$ 4·05); $\lambda_{max.}$ (MeOH) 2600 Å ($\log_{10} \varepsilon$ 4·17); $\lambda_{max.}$ (MeOH + 1 drop of concentrated aqueous hydrochloric acid) 2390 Å ($\log_{10} \varepsilon$ 3·98); $\nu_{max.}$ 1645 and 1550 cm.$^{-1}$ (CO and ring stretch in pyridones).

2-*Methylthioquinolizinium Iodide*.—2-Quinolizone (VI) (0·60 g.) and phosphorus pentasulphide (0·29 g.) were heated for 0·75 hr. at 150° (oil bath). The temperature was then raised to 170° and the pressure reduced to 0·2 mm., a small amount of oily material subliming. The residue was extracted several times with chloroform, and the solution evaporated leaving an oily residue which had the same i.r. spectrum as the sublimate and showed a strong absorption at 1080 cm.$^{-1}$ (C=S stretching). The residue, in the minimum quantity of ethanol, was warmed with methyl iodide. On evaporation and cooling 2-*methylthioquinolizinium iodide* (X; X = I) was obtained. This was suspended in ethanol–acetone and the mixture filtered. Recrystallisation from ethanol–ethyl acetate gave a yellow amorphous solid, m. p. 196—201° (Found: C, 39·6; H, 3·3; N, 4·4. $C_9H_{10}INS$ requires C, 39·4; H, 3·6; N, 4·45%); $\lambda_{max.}$ 2130, 2580, and 3380 Å ($\log_{10} \varepsilon$ 4·55, 4·25, and 4·33). The *picrate* (X; X = picrate) crystallised from ethanol as yellow rhombs, m. p. 183—187° (softening 170°) (Found: C, 47·35; H, 3·05; N, 14·2. $C_{15}H_{12}O_7N_4S$ requires C, 47·55; H, 3·4; N, 13·85%).

Reaction of 2-*Quinolizone with Phosphorus Tribromide*.—Phosphorus tribromide (2 ml.) and 2-quinolizone (VI) (0·300 g.) were boiled under reflux for 2 hr. The excess of phosphorus tribromide was decanted from the cooled mixture, and the brown solid residue washed with dry ether and dissolved in ethanol, giving 2-bromoquinolizinium bromide (VII) (0·17 g. 27%), m. p. 257°, on cooling. The i.r. spectrum of this sample was identical with that described previously.[1] A mixed m. p. showed no depression.

1-*Bromo*-2-*hydroxyquinolizinium Bromide* (XI; X = Br).—Bromine (0·25 g.) in 50% aqueous hydrobromic acid (5 ml.) was added to a stirred solution of 2-hydroxyquinolizinium bromide (II) (0·25 g.) in hydrobromic acid (5 ml.). During the addition a yellow perbromide separated. The mixture was stirred for 1 hr., heated on a water-bath until all the solid had dissolved, and then evaporated to dryness under reduced pressure. The solid was dissolved in water and the solution evaporated. The residue was suspended in ethanol–ethyl acetate, and the mixture filtered giving 1-*bromo*-2-*hydroxyquinolizinium bromide* (0·207 g., 67%), as small rhombs (from ethanol), m. p. 295—297° (decomp., charring above 270°) (Found: C, 35·3; H, 2·55; N, 4·95. $C_9H_7Br_2NO$ requires C, 35·45; H, 2·3; N, 4·6%); $\lambda_{max.}$ 2360, 3050, and 3520 Å ($\log_{10} \varepsilon$ 4·49,4·13, and 3·89). The i.r. spectrum was identical with that of a sample prepared by another route (following Paper).

1-*Bromo*-2-*hydroxyquinolizinium Nitrate* (XI; X = NO_3).—2-Hydroxyquinolizinium bromide (0·25 g.) in 7% nitric acid (5 ml.) was boiled for 15 sec. and cooled immediately in ice-cold water. The pale yellow precipitate (0·225 g., 79%) was crystallised from ethanol to give small needles, m. p. 158—159° (Found: C, 38·2; H, 2·4; N, 9·85. $C_9H_7BrN_2O$ requires C, 37·9; H, 2·5; N, 9·8%). The i.r. spectrum showed a wide band between 1400—1340 cm.$^{-1}$ and a band at 815 cm.$^{-1}$ (NO_3^-). On passage of an aqueous solution of the nitrate through a column of Amberlite IRA 400 (Br) resin the bromide (XI; X = Br) was obtained.

Attempted Formation of 1-*Cyano*-2-*hydroxyquinolizinium Salts*.—2-Hydroxyquinolizinium bromide (II) (0·25 g.) and sodium cyanide (0·35 g.) in 7% nitric acid (5 ml.) were boiled for 15 sec. and cooled in ice–water. The precipitated 2-*hydroxyquinolizinium nitrate* (II; X = NO_3) (0·107 g., 49%) was crystallised from ethanol, forming rhombs, m. p. 188—192° (Found: C, 51·75; H, 4·3. $C_9H_8N_2O_4$ requires C, 51·9; H, 3·85%).

CHEMISTRY DEPARTMENT, UNIVERSITY OF KEELE,
KEELE, STAFFORDSHIRE.

[*Received, October 8th,* 1963.]