Quinolizines. IX. The Properties of 3-Hydroxyquinolizinium Salts[1]

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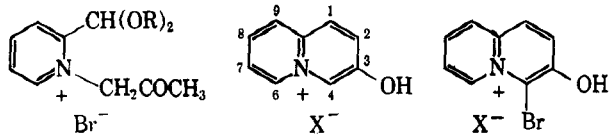
3-Hydroxyquinolizinium salts are readily brominated to give 4-bromo-3-hydroxyquinolizinium salts (**3**). The conversion of the 4-bromo-3-hydroxyquinolizinium salts to 3-hydroxy-4-quinolizone (**5**) and the preparation of two quinolizinium phenol betaines 9 and 10 are described.

In previous papers[1-3] we have reported the synthesis and properties of 1- and of 2-hydroxyquinolizinium salts. As expected, the 1-hydroxyquinolizinium salts were phenolic and underwent electrophilic substitution in position 2,[1,2] while the 2-hydroxyquinolizinium salts behaved more as quinolizones, as has been reported also for the 4-hydroxy series.[4] Electrophilic substitution occurs in all three hydroxyquinolizinium salts[1-3,5] with an ease surprising in a system carrying an over-all positive charge. In the reactions of the 2-hydroxyquinolizinium salts, no electrophilic substitution was observed in the 3-position (behaviour reminiscent of naphthalenes or isoquinolines) and the 3-hydroxyquinolizinium salts represent an interesting case where the "naphthalene" pattern of substitution requires the electrophile to attack the position of expected lower electron density (position 4). In fact, as is shown below, the site of bromination is position 4 and the "naphthalene" pattern is preserved.



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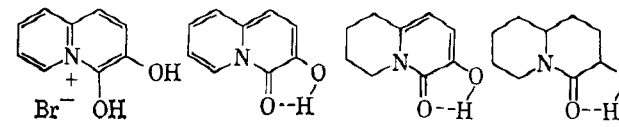
The synthesis of 3-hydroxyquinolizinium bromide (**2**, X = Br) from the diethyl acetal (**1**, R = C_2H_5) has been briefly reported,[6] but no yield was recorded. We have obtained the 3-hydroxyquinolizinium bromide (**2**, X = Br) from the dioxolane (**1**, R = $-CH_2-$) in 96% yield, giving 76% over-all yield from 2-(2-pyridyl)-1,3-dioxolane, and have also prepared the picrate and nitrate.[7] The 3-hydroxyquinolizinium bromide (**2**) reacted readily with bromine in hydrobromic acid to give an 80% yield of a bromohydroxyquinolizinium bromide subsequently shown to have structure **3** (X = Br). This bromohydroxyquinolizinium salt reacted with silver acetate in hot acetic acid to give 3,4-dihydroxyquinolizinium bromide (**4**), presumably *via* the unstable 3-hydroxy-4-acetoxy derivative. Unlike the previously reported 1,2-dihydroxyquinolizinium salt[2] the 3,4-dihydroxyquinolizinium bromide was hydrolyzed by water, losing a proton to give 3-hydroxy-4-quinolizone (**5**) insoluble in water, but soluble in organic solvents. The quinolizone **5** showed strong absorption at 3424 cm.$^{-1}$ (intramolecularly hydrogen-bonded OH) and at 1640 cm.$^{-1}$ (pyridone carbonyl[8]).



4 5 6 7

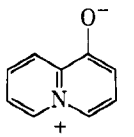
To establish finally the position of the pyridone carbonyl in the quinolizone **5** and hence the site of bromination, the quinolizone **5** was catalytically reduced using Adams catalyst in methanol. Reduction ceased after two molecules of hydrogen had been absorbed; properties of the reduction product (strong infrared absorption at 1640, 1590 and 1540 cm.$^{-1}$ in the pyridone carbonyl region) leave little doubt that it is correctly represented by structure **6**. A similar partial reduction was observed with 2-quinolizone.[8] Reduction of compound **5** using Adams catalyst in glacial acetic acid gave an octahydro derivative **7**. The quinolizidone structure **7** is proved by the presence in the infrared absorption of a strong peak at 1642 cm.$^{-1}$ in the region characteristic for 6-membered lactams.[9] Of the two possible sites for bromination (2- or 4-) the 2,3-disubstituted compound would give rise to 2,3-dihydroxyquinolizidine after the sequence of reactions described above; the infrared spectrum of compound **7** excludes this possibility. Thus bromination of 3-hydroxyquinolizinium salts takes place to a very large extent in the 4-position, confirming the "naphthalene" pattern shown by the 2-hydroxyquinolizinium salts.

Nitration of 1-hydroxyquinolizinium salts gave a series of interesting nitrophenol betaines,[1] and 4-quinolizone has recently been reported to give mono- and dinitro derivatives[5]; 2-hydroxyquinolizinium bromide, however, reacted with dilute nitric acid to give 1-bromo-2-hydroxyquinolizinium nitrate.[3] When 3-hydroxyquinolizinium bromide (**2**, X = Br) was boiled for 1 min. with 10% aqueous nitric acid an orange color formed and discharged; cooling the solution produced in high yield 4-bromo-3-hydroxyquinolizinium nitrate (**3**, X = NO_3). As the bromohydroxyquinolizinium nitrate is almost colorless it seems likely that the bromide ion is oxidized by the nitric acid to free bromine which subsequently attacks the hydroxyquinolizinium cation in position 4; the alternative route (nitration followed by nucleophilic replacement of the nitro group by bromide) seems less likely as no nitration products could be isolated when 3-hydroxyquinolizinium nitrate was heated with 10

(1) For part VIII of this series, see A. Fozard and G. Jones, *J. Chem. Soc.*, 3030 (1964).
(2) A. Fozard and G. Jones, *ibid.*, 2203 (1963).
(3) A. Fozard and G. Jones, *ibid.*, 2760 (1964).
(4) V. Boekelheide and W. G. Gall, *J. Org. Chem.*, **19**, 499 (1954).
(5) B. S. Thyagarajan and P. V. Gopalakrishnan, *Tetrahedron*, **20**, 1051 (1964).
(6) E. Schraufstätter, *Angew. Chem.*, **74**, 874 (1962).
(7) Professor C. K. Bradsher has informed us that he has obtained 3-hydroxyquinolizinium bromide in 48% over-all yield by a similar route, but has made no attempt to isolate the intermediate quaternary pyridinium salt.
(8) A. R. Katritzky and R. A. Jones, *J. Chem. Soc.*, 2947 (1960).
(9) O. E. Edwards and T. Singh, *Can. J. Chem.*, **32**, 683 (1954).

or 35% nitric acid. Attempts to couple benzenediazonium chloride with 3-hydroxyquinolizinium salts were unsuccessful, giving intense colors only in solutions of very high pH. No solid azo product could be isolated.

A notable feature of 2- and 4-hydroxyquinolizinium salts is their conversion into 2- and 4-quinolizone respectively, with loss of one proton. No such simple quinolizone can be obtained from 1- or 3-hydroxyquinolizinium salts, but we have found that on basification of solutions containing 1- or 3-hydroxyquinolizinium bromides chloroform-soluble materials are obtained, and there seems no doubt that these are, respectively, the 1- and 3-hydroxyquinolizinium betaines **8** and **9**. Both are yellow in color and can be recrystallized from organic solvents, though with molecules of water of crystallization which are very tenaciously held. The ultraviolet spectrum of the betaines in nonpolar solvents resembled those of the corresponding hydroxyquinolizinium salts in basic solution. The infrared absorption of the two phenol betaines were similar (with the exception of the 900–600-cm.$^{-1}$ region); both differed from those of the hydroxyquinolizinium salts, lacking the fine structure in the 2500–3000-cm.$^{-1}$ region.



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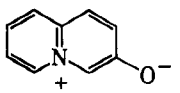

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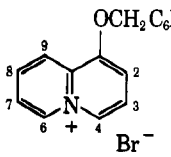

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When a benzene solution of the betaine **8** was boiled with added benzyl bromide a crystalline precipitate was obtained, which analysis showed to be the ether **10**. This formulation was confirmed by the n.m.r. spectrum (D_2O), which showed a doublet at 8.95 (C-6), a doublet at 8.56 (C-4), a five-proton multiplet from 8.4 to 7.55 (C-2, C-3, C-7, C-8, C-9), a five-proton singlet at 7.15 (benzene protons), and a two-proton singlet at 5.12 (benzylic CH_2) (all shifts are given in parts per million from tetramethylsilane).

Experimental

All melting points were determined on a Kofler block. Ultraviolet spectra were determined on a Unicam S.P. 700 spectrophotometer, infrared spectra on a Perkin-Elmer 221 spectrophotometer. Microanalyses were determined by Drs. Weiler and Strauss, Oxford, England.

1-Acetonyl-2-(2-dioxolanyl)pyridinium Bromide (1, R = CH_2).—A solution of 2-(2-dioxolanyl)pyridine (5.5 g.) and bromoacetone (5 g.) in acetone (20 ml.) was allowed to stand at room temperature for 9 days, during which a colorless crystalline precipitate formed. The precipitated pyridinium bromide was found to be sufficiently pure for cyclization (8.5 g., 80%) but a sample was crystallized from ethanol as colorless rhombs, m.p. 158–159°.

Anal. Calcd. for $C_{11}H_{14}BrNO_3$: C, 45.86; H, 4.89; N, 4.86. Found: C, 46.18; H, 5.19; N, 4.63.

3-Hydroxyquinolizinium Salts (2).—A solution of 1-acetonyl-2-(2-dioxolanyl)pyridinium bromide (14 g.) in 50% aqueous hydrobromic acid (130 ml.) was boiled under reflux for 2 hr. Evaporation under reduced pressure gave a yellow powder which was dissolved in water; the resulting solution was again evaporated. The residue was triturated with acetone, filtered, and recrystallized from ethanol–acetone mixtures as colorless rhombs, m.p. 252–254° (lit.[6] m.p. 251°). The yield was 10.56 g. (96%). The infrared spectrum was identical with that supplied by Dr. Schraufstätter. The picrate recrystallized from acetone as microcrystalline yellow needles, m.p. 225–228°.

Anal. Calcd. for $C_{15}H_{10}N_4O_8$: C, 48.15; H, 2.69; N, 14.97. Found: C, 47.94; H, 2.60; N, 15.28.

A solution of 3-hydroxyquinolizinium bromide in water was treated with an exact equivalent of aqueous silver nitrate, filtered from AgBr, and evaporated under reduced pressure to give 3-hydroxyquinolizinium nitrate, recrystallized from ethanol as colorless microneedles, m.p. 229–232° dec.

Anal. Calcd. for $C_9H_8N_2O_4$: C, 51.92; H, 3.87. Found: C, 52.18; H, 4.21.

4-Bromo-3-hydroxyquinolizinium Salts (3).—A solution of bromine (8.0 g.) in 50% aqueous hydrobromic acid (20 ml.) was added slowly with vigorous stirring to a solution of 3-hydroxyquinolizinium bromide (8.0 g.), also in hydrobromic acid (120 ml.). A yellow precipitate formed during the addition, and stirring was continued for 1 hr. after all the bromine had been added. The mixture was heated on a boiling water bath for 2 hr. and then evaporated to dryness under reduced pressure. The residue was suspended in a little ice-cold water and filtered. The 4-bromo-3-hydroxyquinolizinium bromide crystallized from 75% aqueous ethanol as colorless microcrystalline cubes: m.p. 258–260°; 8.57 g. (80%); $\lambda_{max}^{H_2O}$ 2457, 2646, 2717, and 3425 Å. (log ϵ 4.40, 4.30, 4.30, and 4.02).

Anal. Calcd. for $C_9H_8Br_2NO$: C, 35.32; H, 2.64. Found: C, 35.23; H, 2.55.

4-Bromo-3-hydroxyquinolizinium picrate recrystallized from absolute ethanol as yellow needles, m.p. 205°.

Anal. Calcd. for $C_{15}H_9BrN_4O_8$: C, 39.75; H, 2.08. Found: C, 40.05; H, 2.27.

3,4-Dihydroxyquinolizinium Bromide (4).—A suspension of silver acetate (4.1 g.) and 4-bromo-3-hydroxyquinolizinium bromide (3.5 g.) in glacial acetic acid (200 ml.) was boiled under reflux with vigorous stirring for 3 days. The cooled mixture was filtered and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in 50% aqueous hydrobromic acid, heated on a water bath for 0.5 hr., then evaporated to dryness under reduced pressure. The residue was crystallized from absolute ethanol–ethyl acetate with the use of charcoal giving 3,4-dihydroxyquinolizinium bromide, m.p. 175–180° dec., as light brown cubes (1.7 g., 62%): λ_{max}^{EtOH} 2220, 2545, and 3730 Å. (log ϵ 4.24, 4.14, and 4.03).

Anal. Calcd. for $C_9H_8BrNO_2$: C, 44.65; H, 3.33; N, 5.78. Found: C, 44.69; H, 3.53; N, 6.22.

3-Hydroxy-4-quinolizone (5).—3,4-Dihydroxyquinolizinium bromide (1.00 g.) was treated with water (5 ml.) and the precipitate obtained was recrystallized from aqueous ethanol as yellow needles: 0.48 g. (73%); m.p. 197–200°; λ_{max}^{EtOH} 2220, 2530, and 3730 Å. (log ϵ 4.25, 4.15, and 4.04); $\nu_{max}^{CCl_4}$ 3429 (hydrogen bonded OH, unchanged by dilution) and 1640 (pyridone carbonyl) cm.$^{-1}$.

Anal. Calcd. for $C_9H_7NO_2$: C, 67.07; H, 4.38. Found: C, 67.13; H, 4.48.

3-Hydroxy-6,7,8,9-tetrahydro-4-quinolizone (6).—A solution of 3-hydroxy-4-quinolizone (0.40 g.) in 95% ethanol was reduced with Adams catalyst (0.075 g.) at room temperature and pressure until uptake of hydrogen ceased (2 moles). Filtration and evaporation of the filtrate gave 3-hydroxy-6,7,8,9-tetrahydro-4-quinolizone, purified by sublimation as colorless rhombs: m.p. 182–186°; 0.23 g. (56%); λ_{max}^{EtOH} 2470 and 3155 Å. (log ϵ 3.64 and 3.92); $\lambda_{max}^{100\%\ H_2SO_4}$ 2280 and 3030 Å. (log ϵ 3.78 and 4.01); ν_{max}^{KBr} 3200 (hydrogen-bonded OH), 1640, 1590, and 1540 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.60; H, 6.65; N, 8.31.

3-Hydroxy-4-quinolizidone (7).—A solution of 3-hydroxy-4-quinolizone (0.60 g.) in purified glacial acetic acid (25 ml.) was reduced with Adams catalyst (0.15 g.) at room temperature and atmospheric pressure until uptake of hydrogen ceased (4 moles). Filtration and evaporation gave an oily residue which crystallized on trituration with petroleum ether (0.305 g., 50%). It was purified by repeated sublimation giving colorless needles: m.p. 70° (softening at 60°); $\nu_{max}^{CCl_4}$ 3484 (intramolecularly bonded OH) and 1642 cm.$^{-1}$ (6-membered lactam carbonyl).

Anal. Calcd. for $C_9H_{15}NO_2$: C, 63.88; H, 8.94; N, 8.28. Found: C, 63.81; H, 8.73; N, 8.72.

Treatment of 3-Hydroxyquinolizinium Bromide with Nitric Acid.—A solution of 3-hydroxyquinolizinium bromide (0.6 g.) in 10% aqueous nitric acid (7 ml.) was boiled for 1 min. during which the solution became brown, then paled to yellow. After

cooling the solution in ice–water almost pure 4-bromo-3-hydroxyquinolizinium nitrate (**3**, X = NO_3) was obtained (0.57 g., 75%) crystallizing from ethanol as colorless needles, decomposing at 135–140°, melting above 200°.

Anal. Calcd. for $C_9H_7BrN_2O_4$: C, 37.64; H, 2.46; N, 9.76. Found: C, 38.13; H, 2.49; N, 9.32.

When a solution of the nitrate was passed through Amberlite IRA 400 (Br), 4-bromo-3-hydroxyquinolizinium bromide was obtained, identical with that obtained by direct bromination of 3-hydroxyquinolizinium bromide.

1-Hydroxyquinolizinium Betaine (**8**).—Saturated aqueous sodium carbonate solution (5 ml.) was added to 1-hydroxyquinolizinium bromide (1.00 g.) dissolved in water (2 ml.). Effervescence occurred and needles of the hydrated betaine were precipitated. The almost pure betaine was dried for several hours under reduced pressure (0.415 g., 58%). It sublimed as a yellow solid: m.p. 187–191°; $\lambda_{max}^{95\%\ EtOH}$ 2660, 3740 (sh), and 4000 Å. (log ε 3.91, 3.91, and 3.94); $\lambda_{max}^{CHCl_3}$ 2500, 2780, 3820, and 4310 Å. (log ε 3.85, 3.85, 3.85, and 3.85).

Anal. Calcd. for $C_9H_7NO \cdot H_2O$: C, 66.24; H, 5.56; N, 8.58. Found: C, 65.69; H, 5.57; N, 8.61.

3-Hydroxyquinolizinium Betaine (**9**).—A saturated solution of aqueous sodium carbonate (15 ml.) was added to 3-hydroxyquinolizinium bromide (1.00 g.) dissolved in water (2 ml.). Effervescence and the formation of yellow oily droplets were noticed during the addition. The mixture was continuously extracted with chloroform for 12 hr., and the dried (Na_2SO_4) chloroform extracts were evaporated. The oily residue was dissolved in acetone and the acetone was evaporated to small bulk. Cooling gave crystals of the betaine which recrystallized from acetone as yellow needles: m.p. 143–146°; 0.39 g. (48%); $\lambda_{max}^{CHCl_3}$ 2500, 2690, 2780, and 3620 Å. (log ε 4.38, 4.36, 4.36, and 4.18). The analysis specimen was dried overnight at room temperature (0.01 mm.) and then for 6 hr. at 100° (0.0005 mm.).

Anal. Calcd. for $C_9H_7NO \cdot 2A_2O$: C, 59.66; H, 6.12; N, 7.73. Found: C, 60.10; H, 6.31; N, 8.06.

1-Benzyloxyquinolizinium Bromide (**10**).—A solution of 1-hydroxyquinolizinium betaine (**8**, 0.175 g.) in benzene (40 ml.) was evaporated to approximately 10 ml. Benzene (40 ml.) was added followed by benzyl bromide (0.29 g.) and the mixture was boiled under reflux for 4 hr. The crystalline solid which had separated was filtered off and recrystallized from ethanol–ethyl acetate as colorless needles: m.p. 167–170°; 0.156 g. (38%); $\lambda_{max}^{H_2O}$ 2460 and 3500 Å. (log ε 4.33 and 4.27).

Anal. Calcd. for $C_{16}H_{14}BrNO \cdot 2H_2O$: C, 54.55; H, 5.15; N, 3.97. Found: C, 54.68; H, 4.98; N, 3.87.

The ether **8** gave a precipitate with a silver nitrate–nitric acid mixture but gave no color with neutral ferric chloride solution.

Jervine. XIV. Isojervin-11β-ol and Related Reduction Products of Isojervine

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Isojervine (Ia) is reduced by lithium borohydride to isojervin-11β-ol (IIa), the 3,23,N-triacetate of which (IIb) reverted on oxidation to the triacetate Ib of the parent ketone. N-acetylisojervine (Ic) yielded in this reduction, however, a crystalline mixture containing, in addition to the expected N-acetyl-isojervin-11β-ol (IIc), a more dextrorotatory 11β-ol, the triacetate of which on oxidation gave a ketone resembling in its ultraviolet characteristics the unconjugated ketone VI (triacetyl-8β,9α-dihydroisojervine) rather than Ic, but differing from both VI and Ic by its very high dextrorotation. This ketone was eventually assigned the 8ξ,9ξ-dihydro structure V on the basis mainly of the ultraviolet characteristics of the α,β-unsaturated enone IX obtained from Vb *via* its 5,6-dihydro derivative VII and the 17,17a-epoxide VIII.

Long before the structure of isojervine (Ia) was established[1-3] we had studied the reduction of this compound with borohydrides in order to make sure that the 11-keto group was part of the chromophor responsible for its abnormal ultraviolet absorption spectrum. Since lithium borohydride gave better yields of the resulting crystalline base (m.p. 219°, $[\alpha]_D$ −54°) than sodium borohydride, it was used in all subsequent experiments. That the reduction product is isojervin-11β-ol (IIa, m.p. 217–219°, recently also reported by Masamune, *et al.*,[2] with m.p. 210–211°) is evidenced (1) by the lack of specific absorption in the region 220–360 mμ; (2) the presence of only weak bands at 6.05 and 6.20 μ in the double bond stretching vibration region of the infrared spectrum; (3) the formation on mild acetylation of a triacetate (IIb, m.p. 186°, $[\alpha]_D$ +24°) which with alkali gave the N-acetyl derivative IIc (m.p. 211°, $[\alpha]_D$ +6°) and on Jones oxidation[4] reverted to triacetylisojervine (Ib) (Chart I).

Isojervin-11β-ol and its acetylated derivatives give a strong Rosenheim reaction (purple), and on addition of dilute hydrochloric acid to their alcoholic solutions produce a rose-colored, orange-fluorescing pigment. This instability to acid is also evident in the formation of yellow decomposition products on chromatography of the acetates on acid-washed or neutral alumina. These color reactions are not dependent only, however, on the presence of the allylic alcohol grouping in II, but, as will appear later, also of the 5,6-double bond. On the other hand, isojervin-11β-ol does not display the characteristic instability of isojervine towards strong alkali which manifests itself in the formation of a deep red pigment.

It was then surprising to find, in the face of these straightforward results, that the lithium borohydride reduction of N-acetylisojervine (Ic) did not lead to the N-acetylisojervin-11β-ol IIc, m.p. 211°, but to higher-melting, more dextrorotatory products (m.p. 230–232°, $[\alpha]_D$ +65 to 75°) which on acetylation yielded triacetates, m.p. 183–186°, $[\alpha]_D$ +78 to 98°. It soon became clear that these new acetylated reduction products were mixtures, respectively, of the normal triacetyl- and N-acetylisojervin-11β-ols IIb and IIc and the corresponding derivatives of a more dextrorotatory entity which to judge from the analytical results was isomeric with the normal isojervin-11β-ol IIa. These derivatives (triacetate, m.p. 162–167°, $[\alpha]_D$ +133°; N-acetyl derivative, m.p. 240–241°, $[\alpha]_D$ +132°) differed from the crystalline mixtures originally obtained by no longer giving the color reactions char-

(1) (a) O. Wintersteiner and M. Moore, *Tetrahedron Letters*, 795 (1962); (b) *J. Org. Chem.*, **29**, 262 (1964).

(2) T. Masamune, M. Takasugi, H. Suzuki, S. Kawahara, M. Godha, and T. Irie, *Bull. Chem. Soc. Japan*, **35**, 1749 (1962).

(3) W. G. Dauben, W. W. Epstein, M. Tanabe, and B. Weinstein, *J. Org. Chem.*, **28**, 293 (1963).

(4) K. Bowden, I. M. Heilbron, E. R. H. Jones, and C. L. Weedon, *J. Chem. Soc.*, 39 (1946); C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).