gave 1.2 g., m.p. 76–78°, which was identical by melting point, mixture melting point, and infrared spectrum with the material prepared by method A.

2,5-Dimethoxybenzenesulfonyl Chloride (17).—2,5-Dimethoxybenzenesulfonic acid was prepared by the method of Baker and Evans[8] and converted to its potassium salt. Interaction of the potassium salt with phosphorus pentachloride gave 2,5-dimethoxybenzenesulfonyl chloride which, after recrystallization from chloroform–petroleum ether (b.p. 60–80°), melted at 115–116°.

Anal. Calcd. for $C_8H_9ClO_4S$: C, 40.6; H, 3.8; S, 13.6. Found: C, 41.0; H, 4.1; S, 13.5.

2,5-Dimethoxybenzenethiol (18).—2,5-Dimethoxybenzenesulfonyl chloride was reduced with zinc and sulfuric acid as described[9] for the reduction of benzenesulfonyl chloride. The product had b.p. 142° at 18 mm. (lit.[7] b.p. 138–140° at 20 mm.).

2,5-Dimethoxy-1-(1′-phenyl-5′-tetrazolylthio)benzene (16).—A solution of 3.44 g. of 2,5-dimethoxybenzenethiol in 20 ml. of 1 *N* ethanolic potassium hydroxide was added to 4.5 g. of 5-bromo-1-phenyltetrazole in ethanol. The mixture was refluxed for 14 hr., cooled, and filtered to remove potassium bromide. The product (5.5 g., 88%) was recrystallized from ethanol, m.p. 116–117°.

Anal. Calcd. for $C_{15}H_{14}N_4O_2S$: C, 57.3; H, 4.5; N, 17.8. Found: C, 57.5; H, 4.3; N, 17.6.

5-Phenoxy-1-phenyltetrazole (19).—A mixture of 1.88 g. of phenol, 4.50 g. of 5-bromo-1-phenyltetrazole, 100 ml. of ethanol, and 20 ml. of 1 *N* potassium hydroxide in ethanol was refluxed overnight, the ethanol was evaporated, and the residue was extracted with chloroform. This solution was washed with cold 5% sodium hydroxide and then with water. The chloroform was removed by evaporation and the oil was dissolved in ether from which white crystals were obtained. Two recrystallizations from ethanol gave 0.95 g. (20%), m.p. 124.5–126.5°.

Anal. Calcd. for $C_{13}H_{10}N_4O$: C, 65.5; H, 4.2; N, 23.5. Found: C, 65.3; H, 4.3; N, 23.8.

Hydrolysis of 5-Phenoxy-1-phenyltetrazole (19).—A mixture of 0.66 g. of 5-phenoxy-1-phenyltetrazole (19) and 20 ml. of 1 *N* sodium hydroxide was refluxed overnight to give a solution. Filtration, followed by acidification with dilute hydrochloric acid, gave a white precipitate which was washed with water to remove the odor of phenol. The dried product weighed 0.35 g. (79%) and melted at 188–190°. An infrared spectrum of this compound was identical with that of a known sample of 5-hydroxy-1-phenyltetrazole (8).

Acknowledgment.—The authors gratefully acknowledge the assistance of Mr. C. M. Combs and Dr. J. K. O'Loane in the preparation and interpretation of the n.m.r. spectra.

(8) W. Baker and C. Evans, *J. Chem. Soc.*, 372 (1938).

(9) R. Adams and C. S. Marvel, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1958, p. 504.

The Synthesis of a Pyrido[1,2-*a*]azepine. A New Heterocyclic System[1]

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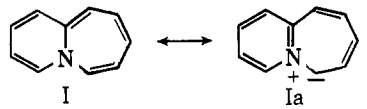
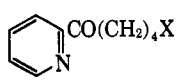
The cyclization of 2-(5′-ethoxyvaleryl)pyridine (II) gives the cyclic ketone (IV) which has been converted into the 9-bromo- and 9,9-dibromo-10,10-dihydroxypyridoazepinium salts (V and VI). Boiling acetic anhydride converted the dibromo compound (VI) into 10-acetoxy-9-bromo-6H-pyrido[1,2-*a*]azepinium bromide (IX) and bromination of this gave 7,9- dibromo-6H-pyrido[1,2-*a*]azepinium bromide (XII), converted by base into 7,9-dibromo-10-hydroxypyrido[1,2-*a*]azepine (XIII). The hydrogenations of the azepine (XIII) to a 2-pyridylpentanal acetal (XVI) and to the 10-hydroxytetrahydropyridoazepinium salt (XV) are described.

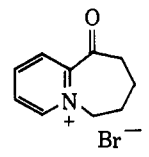
While the indolizine and quinolizinium systems are well known, and while there has been much recent interest in azepine chemistry, no attempts to prepare a pyrido[1,2-*a*]azepine system (I) have yet been reported. Although a fully aromatic form (with ten π-electrons and all atoms trigonal) cannot be achieved, some stabilization should be achieved by virtue of the carbon betaine structures (such as Ia) and still more stabilization was expected in the 6-, 8-, or 10-hydroxy systems. As we have previously devised a satisfactory method for the synthesis of a 1-hydroxyquinolizinium salt,[2] we decided to apply a modified version of this synthesis to the production of a 10-hydroxypyrido[1,2-*a*]azepine, thus obtaining the first member of this heterocyclic system.



I Ia



II, X = OC_2H_5
III, X = Br



IV

The starting material for the synthesis was the 2-pyridyl ketone (II) obtained from 2-cyanopyridine and 4-ethoxybutylmagnesium bromide. In the quinolizinium series the cyclization of a similar ketone was achieved by cleavage of the ether with hydrobromic acid and cyclization of the crude bromo ketone so obtained in refluxing chloroform. Only a poor yield of cyclic ketone (IV) was obtained in this manner, but the crude bromo ketone (III) was satisfactorily cyclized by heating without solvent to 130°. The infrared and ultraviolet absorption of the cyclic ketone (IV) were similar to those of 1-oxo-1,2,3,4-tetrahydroquinolizinium bromide,[3] notably in the position of the carbonyl stretching frequency at 1700 cm.$^{-1}$. Bromination of the cyclic ketone (IV) with bromine in concentrated hydrobromic acid proceeded readily, giving a mono- or dibromo product depending on the amount of bromine used. Neither brominated product showed more than vestigial carbonyl absorption in the infrared region and the ultraviolet spectra resemble that of a

(1) Presented before the Organic Chemical Division at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1964.

(2) A. Fezard and G. Jones, *J. Chem. Soc.*, 2203 (1963).

(3) E. E. Glover and G. Jones, *ibid.*, 1750 (1958). The quinolizinium bromide has λ_{max}^{EtOH} 2350 and 2750 Å. ($\log_{10}\epsilon$ 3.62 and 3.89); the shift of the second maximum to shorter wave length (2680 Å.) in the ketone (IV) is in accord with the known lowering of conjugation when a chromophore attached to an aromatic ring is contained in a fused seven-membered ring [for an example, see W. R. Remington, *J. Am. Chem. Soc.*, **67**, 1838 (1945), where the spectra of N-methyltetrahydroquinoline and N-methylhomotetrahydroquinoline are compared].

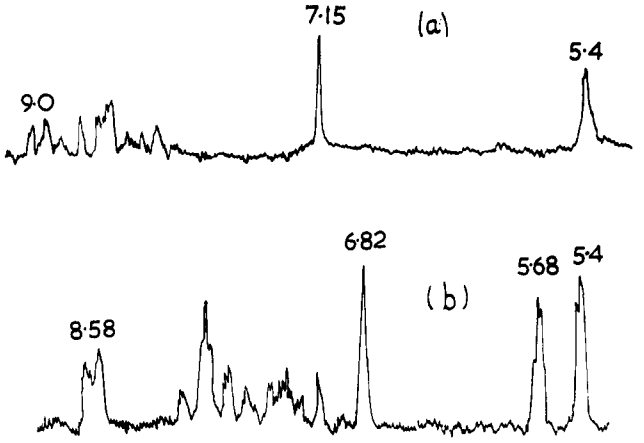
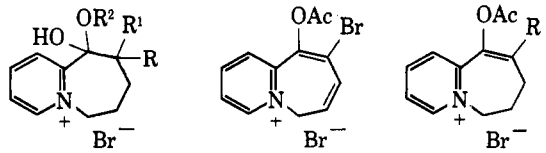


Figure 1.—(a) N.m.r. spectrum of 7,9-dibromo-10-hydroxy-6H-pyrido[1,2-*a*]azepinium bromide (XII) in deuterium oxide. (b) N.m.r. spectrum of 7,9-dibromo-10-hydroxypyrido[1,2-*a*]-azepine (XIII) in deuteriochloroform. Chemical shifts are given in parts per million from tetramethylsilane.

simple pyridinium system with no additional conjugation. Both brominated products showed strong absorption in the 3100–3250-cm.$^{-1}$ region, and this, combined with analyses which showed the presence of two oxygen atoms, led to the formulation of the bromination products as the hydrates (V and VI). Recrystallization of the 9-bromo hydrate (V) or the 9,9-dibromo hydrate (VI) from ethanol led to considerable changes in melting point and infrared absorption (notably in a shift of the O–H stretching frequency and decrease in intensity, accompanied by changes in the 1150–1000-cm.$^{-1}$ region) and the recrystallized products gave analysis values consistent with the formation of the hemiketals (VII and VIII).

The introduction of the α,β-unsaturation was achieved in the quinolizinium series by heating an α,α-dibromo ketone without solvent or in boiling acetic anhydride. When the dibromo ketone hydrate (VI) was heated without solvent, hydrogen bromide was copiously evolved, but the residue was uncrystallizable. Boiling acetic anhydride converted the dibromo compound (VI) into a new crystalline salt, analyzing for $C_{12}H_{11}Br_2NO_2$. The ultraviolet spectrum showed increased conjugation, and the infrared spectrum showed no absorption from 3300–3600 cm.$^{-1}$. Strong absorption at 1780 and at 1165 cm.$^{-1}$ characteristic of an enol acetate led to the formulation of the dehydrobrominated material as 9-bromo-10-acetoxy-6H-pyrido-[1,2-*a*]azepinium bromide (IX). Boiling acetic anhydride converted the monobromo compound (V) into 9-bromo-10-acetoxy-6H-7,8-dihydropyrido[1,2-*a*]azepinium bromide (X), and similar treatment of the unbrominated ketone (IV) gave the enol acetate (XI). These enol acetates showed strong absorption at 1780 (X) and 1760 cm.$^{-1}$ (XI) in the carbonyl region and at 1175 (X) and 1210 cm.$^{-1}$ (XI) in the C–O stretching region.



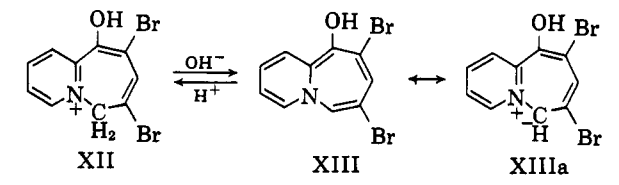
V, R = R² = H, R¹ = Br
VI, R = R¹ = Br, R² = H
VII, R = H, R¹ = Br, R² = C_2H_5
VIII, R = R¹ = Br, R² = C_2H_5

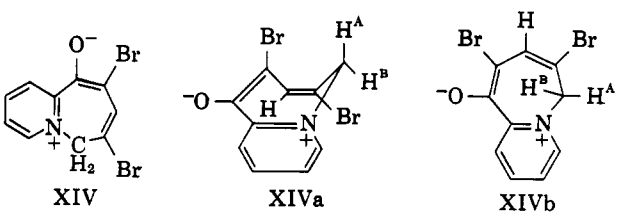
IX

X, R = Br
XI, R = H

Hydrolysis of the bromoacetoxy compound (IX) in aqueous hydrobromic acid led to the development of the long-wave-length maximum expected for the conjugated enone system, but no crystalline compounds could be isolated. Treatment of the hydrolysis mixture with bromine gave a new compound of molecular formula $C_{10}H_8Br_3NO$, containing one bromide ion and two covalently bound bromine atoms. No carbonyl absorption was shown, and the compound showed an absorption maximum at 411 mμ (indicating formation of an increased conjugated system) with a large bathochromic shift on basification. These observations (together with a green ferric chloride color test) led to the formulation of the new compound as 7,9-dibromo-10-hydroxy-6H-pyrido[1,2-*a*]azepinium bromide (XII); this is further confirmed by the n.m.r. spectrum of the salt in deuterium oxide which is shown in Figure 1a. The four-proton multiplet from 9.0–8.0 p.p.m. includes a one-proton doublet at 9.0 p.p.m. assigned to H-4. The singlet at 7.15 is assigned to H-8 and the two-proton broad singlet at 5.4 p.p.m. to the methylene group at C-6.

As mentioned above, basification of aqueous solutions of compound (XII) gave deep red colors, with absorption maxima above 5000 Å. When a saturated solution of sodium carbonate was added to a solution of the azepinium bromide (XII) and the mixture was allowed to stand, a deep red crystalline solid separated; although unstable to recrystallization, the crystals could be washed and dried and gave consistent analyses for the pyrido[1,2-*a*]azepine (XIII ↔ XIIIa).





The formation of the pyridoazepine (XIII) is reversible; a solution of the azepine in water or in dilute acid shows the spectral chracteristics of the azepinium bromide (XII); the bromide (XII) could be isolated from an ethanol solution of the azepine (XIII) to which a few drops of hydrobromic acid had been added. The variation in ultraviolet absorption shown by the pyridoazepine (XIII) in different solvents is striking and is shown in Table I.

The formulation of the deep red substance as the pyrido[1,2-*a*]azepine (XIII ↔ XIIIa) rather than as the phenolic betaine (XIV) is based principally on the n.m.r. spectrum of a deuteriochloroform solution, shown in Figure 1b. Three sharply defined singlets can be seen, each equivalent to one proton, at 5.4, 5.68, and 6.82 p.p.m. with only minor splitting (J = <1 c.p.s.). It is difficult to correlate this pattern

TABLE I

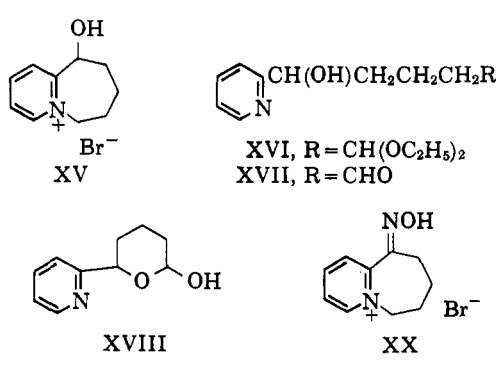
ULTRAVIOLET ABSORPTION OF THE AZEPINE (XIII) AND AZEPINIUM BROMIDE (XII) IN VARIOUS SOLVENTS

Compound	Solvent	Temp., °C.	λ_{max} ($\log_{10}\epsilon$)
XIII	$CHCl_3$ or $C_2H_4Cl_2$	19	270 (...),[a] 518 (2.93)
XIII	$C_2H_4Cl_2$	57	270 (...)[a]
XIII	H_2O	19	261 (3.87), 316 (3.67), 420 (3.59)
XIII	C_2H_5OH	19	262 (3.91), 324 (3.69), 455 (3.62)
XII	H_2O	19	258 (3.98), 311 (3.78), 410 (3.74)
XII	H_2SO_4 (concd.)	19	257 (...),[a] 354 (...)[a]

[a] Extinction coefficient was not obtained.

with the structure XIV having a methylene group at C-6. If the protons marked H^A and H^B in XIVa and XIVb were nonequivalent, they should show considerable splitting; on the other hand, if the barrier between the forms XIVa and XIVb is low, a singlet should result as is shown in the case of the pyrido[1,2-*a*]azepinium bromide (XII) (Figure 1a). Attempts to exchange one of the protons for deuterium have so far been unsuccessful.

Hydrogenation of the azepinium bromide (XII) gave 10-hydroxy-6H-7,8,9,10-tetrahydropyrido[1,2-*a*]-azepinium bromide (XV) also obtained by reduction of the pyridoazepinium ketone (IV), so that the bicyclic nature of the azepinium bromide (XII) is established. Hydrogenation of the azepine (XIII) in neutral solution would give rise to hydrogen bromide and hence would be equivalent to hydrogenation of the azepinium bromide (XII). Accordingly the azepine was hydrogenated in ethanol solution containing a few drops of sodium hydroxide. The product of hydrogenation was a yellow oil, purified by distillation; the infrared spectrum showed the presence of a secondary alcohol and an acetal (strong C–O stretching bands at 1120 and 1060 $cm.^{-1}$) and was identical with a synthetic specimen of 5-(2′-pyridyl)-5-hydroxypentanal diethyl acetal (XVI). The pyridyl acetal was synthesized by interaction of pyridine-2-aldehyde and the Grignard reagent from 4-chlorobutanal diethyl acetal. Attempts to isolate the free hydroxyaldehyde (XVII) by hydrolysis led to the formation of 2-(2′-pyridyl)-6-hydroxytetrahydropyran (XVIII). The formation of the pyridyl acetal (XVI) from the azepine is assumed to proceed *via* a monocyclic form (XIX) with successive base-catalyzed addition of ethanol and elimination of hydrogen bromide, as shown in Scheme I. The uptake of hydrogen was three molecules per molecule of azepine, in accord with Scheme I or some simple variant upon it.

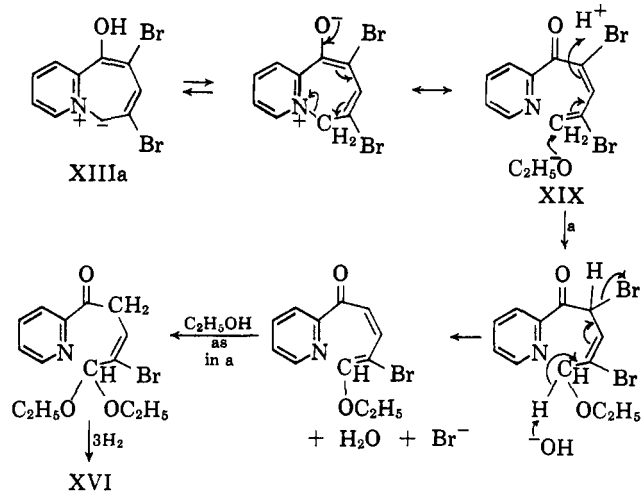


XV XVI, R = $CH(OC_2H_5)_2$; XVII, R = CHO

XVIII XX

SCHEME I

SUGGESTED ROUTE FOR FORMATION OF XVI



Hydrogenation of the pyridoazepine (XIII) in ethanol with added sodium acetate gave a mixture of pyridines and some of the hydroxy compound (XV).

The pyrido[1,2-*a*]azepine system should possess some of the properties of a conjugated polyene and, in view of the reported[4] addition of dimethyl acetylene dicarboxylate to indolizine to give a cyclazine, the interaction of the pyrido[1,2-*a*]azepine (XIII) with tetracyanoethylene (TCNE) and with dimethylacetylene dicarboxylate was examined. A solution of TCNE reacts with one of the azepine (XIII) to give a vivid blue color (presumably a π-complex) which fades on standing with concomitant precipitation of the insoluble material, analyzing for a 1:1 adduct; the results with acetylene dicarboxylic ester were ambiguous.

The oxime bromide (XX) was prepared with a view to performing a Beckmann rearrangement with ring enlargement to the pyrido[1,2-*a*][1,3]diazocine system. Attempts to perform such a Beckmann rearrangement have been unsuccessful.

Experimental[5]

4-Ethoxybutyl Bromide.—Prepared from tetramethylene glycol in 48% yield by an analogous procedure to that described for 3-ethoxypropyl bromide,[6] this bromide had b.p. 167–172° (750 mm.) (lit.[7] b.p. 169°).

2-(5′-Ethoxyvaleryl)pyridine (II).—The Grignard reagent from 4-ethoxybutyl bromide (70 g.) and magnesium (12 g.) in ether (650 ml.) was added slowly to 2-cyanopyridine (40 g.) in ether (300 ml.) under an atmosphere of nitrogen. Vigorous stirring was maintained throughout the addition. After standing overnight, the complex was hydrolyzed by the addition of 5 *N* aqueous hydrochloric acid and then made alkaline with ammonia (s.g. 0.88). The ether layer was separated and dried (sodium sulfate), and the ether removed. The residue was distilled under reduced pressure under nitrogen and the product was collected at 158–162° (10 mm.) to yield 42.6 g. (54%) of 2-(5′-ethoxyvaleryl)-

(4) A. Galbraith, T. Small, and V. Boekelheide, *J. Org. Chem.*, **24**, 582 (1959).

(5) Infrared spectra were determined on a Perkin-Elmer 221 instrument. N.m.r. spectra were performed on a Varian A-60 or Perkin-Elmer 60-Mc. instrument and are recorded in parts per million from a tetramethylsilane standard. Ultraviolet and visible spectra were determined on a Unicam S.P. 700 spectrometer and melting points on a Kofler block.

(6) E. P. Anderson, J. V. Crawford, and M. L. Sherrill, *J. Am. Chem. Soc.*, **63**, 1964 (1941).

(7) G. A. R. Kon, R. P. Linstead, and C. Simons, *J. Chem. Soc.*, 814 (1937).

pyridine: $\lambda_{max}^{95\%\ EtOH}$ 230 and 270 mμ ($\log_{10}$ ε 3.94 and 3.68), $\nu_{max}^{liq\ film}$ 1710 (C=O) cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.58; H, 8.38; N, 6.82.

10-Oxo-7,8,9,10-tetrahydro-6H-pyrido[1,2-*a*]azepinium Bromide (IV).—2-(5-Ethoxyvaleryl)pyridine (II) (20.0 g.) in 50% aqueous hydrobromic acid (200 ml.) was boiled under reflux for 1 hr. (The ethyl bromide which formed was periodically allowed to escape by removal of the condenser.) Evaporation under reduced pressure gave a residue which was dissolved in water and treated dropwise with saturated aqueous sodium carbonate solution until neutral. The liberated bromoamine was extracted with chloroform after each addition of base. The chloroform extracts were dried (sodium sulfate) and the chloroform was removed. The residue was heated for 1 hr. at 130–140° (oil bath) and cooled, and the viscous solid was dissolved in absolute ethanol. Evaporation of the solution to small bulk followed by cooling gave a crystalline solid which was suspended in acetone and filtered to give 12.75 g. (54%) of the cyclic ketone bromide (IV), m.p. 151–154°. Recrystallization from ethanol–acetone gave rhombs: m.p. 154–156°, $\lambda_{max}^{H_2O}$ 268 mμ ($\log_{10}$ ε 3.83), ν_{max}^{Nujol} 1700 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{12}BrNO$: C, 49.59; H, 5.00; N, 5.80. Found: C, 49.40; H, 5.10; N, 6.19.

The picrate prepared by addition of aqueous sodium picrate to the bromide crystallized from ethanol as yellow needles, m.p. 116–117°.

Anal. Calcd. for $C_{16}H_{14}N_4O_8$: C, 49.23; H, 3.62; N, 14.36. Found: C, 48.88; H, 3.67; N, 14.32.

9-Bromo-10,10-dihydroxy-7,8,9,10-tetrahydro-6H-pyrido[1,2-*a*]azepinium Bromide (V).—To a stirred solution of the cyclic ketone bromide (1.0 g.) in 50% aqueous hydrobromic acid (25 ml.) was added bromine (0.68 g.) in hydrobromic acid (10 ml.). An oily yellow solid came out of solution during the addition and stirring was continued for 0.25 hr. after the bromine had been added. The mixture was heated on a boiling-water bath for 20 min. and then evaporated under reduced pressure, giving a solid which was dissolved in water and re-evaporated. The solid was suspended in acetone and filtered to give 1.2 g. (85%) of the monobromo compound (V), recrystallized from an 80% acetone–water solution as blunt needles: m.p. 135.5–136°, $\lambda_{max}^{H_2O}$ 267 mμ ($\log_{10}$ ε 3.72), ν_{max}^{Nujol} 3250 cm.$^{-1}$ (H-bonded OH).

Anal. Calcd. for $C_{10}H_{13}Br_2NO_2$: C, 35.40; H, 3.86; N, 4.13. Found: C, 35.57; H, 3.94; N, 4.61.

9-Bromo-10-ethoxy-10-hydroxy-7,8,9,10-tetrahydro-6H-pyrido-[1,2-*a*]azepinium Bromide (VII).—VII was prepared by recrystallization of the monobromo bromide (V) from ethanol–ethyl acetate as colorless blunt needles: m.p. 132–133°, $\lambda_{max}^{H_2O}$ 267 mμ ($\log_{10}$ ε 3.86), ν_{max}^{Nujol} 3120 cm.$^{-1}$ (H-bonded OH).

Anal. Calcd. for $C_{12}H_{17}Br_2NO_2$: C, 39.25; H, 4.66; N, 3.82. Found: C, 39.28; H, 4.77; N, 3.29.

9-Bromo-10-acetoxy-7,8-dihydro-6H-pyrido[1,2-*a*]azepinium Bromide (X).—A solution of the bromodihydroxy bromide (V, 1.0 g.) in acetic anhydride (120 ml.) was boiled under reflux for 1 hr. Cooling followed by evaporation to dryness gave an oily residue which could be crystallized after trituration with acetone. Crystallization from ethanol–acetone gave 0.62 g. (49%) of microcrystalline rhombs: m.p. 183–183.5°, ν_{max}^{Nujol} 1780 (acetyl C=O) and 1175 cm.$^{-1}$ (C—O stretching).

Anal. Calcd. for $C_{12}H_{13}Br_2NO_2$: C, 39.66; H, 3.61; N, 3.86. Found: C, 39.92; H, 3.78; N, 3.84.

9,9-Dibromo-10,10-dihydroxy-7,8,9,10-tetrahydro-6H-pyrido-[1,2-*a*]azepinium Bromide (VI).—To a stirred solution of the ketone bromide (IV, 10.0 g.) in 50% aqueous hydrobromic acid (100 ml.) was added bromine (15.0 g.) in hydrobromic acid (40 ml.). An oily yellow solid came out of solution during the addition. Stirring was continued for 15 min. after the bromine had been added and the mixture was then warmed on a boiling-water bath for 20 min. Evaporation under reduced pressure gave a fawn-colored solid which was treated with water and re-evaporated. The solid was suspended in a 50% acetone–water mixture and filtered giving 13.85 g. (80%) of the dibromo compound, m.p. 165° dec. A portion crystallized from water for analysis gave colorless microcrystalline needles: m.p. 163.5–164.5° dec.; $\lambda_{max}^{H_2O}$ 267 mμ ($\log_{10}$ ε 3.88); ν_{max}^{Nujol} 3100 (OH), 1150, and 1045 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{12}Br_3NO_2$: C, 28.72; H, 2.84; N, 3.39. Found: C, 28.62; H, 2.80; N, 3.63.

9,9-Dibromo-10-ethoxy-10-hydroxy-7,8,9,10-tetrahydro-6H-pyrido[1,2-*a*]azepinium Bromide (VIII).—VIII was obtained as small colorless rhombs, m.p. 110–111°, by recrystallization of the dibromo compound (VI) from ethanol–ethyl acetate: $\lambda_{max}^{H_2O}$ 270 mμ ($\log_{10}$ ε 3.90), ν_{max}^{Nujol} 3300 (OH) and 1070 cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{16}Br_3NO_2 \cdot H_2O$: C, 31.08; H, 3.92; N, 3.02. Found: C, 30.54; H, 3.62; N, 3.39.

The 10-methoxy derivative was similarly prepared by recrystallization of the dibromodihydroxy compound (VI) from methanol–ethyl acetate as colorless rhombs: m.p. 107–109°, $\lambda_{max}^{H_2O}$ 265 mμ ($\log_{10}$ ε 3.76).

Anal. Calcd. for $C_{11}H_{14}Br_3NO_2 \cdot H_2O$: C, 29.35; H, 3.60; N, 3.11. Found: C, 29.19; H, 4.15; N, 2.81.

9-Bromo-10-acetoxy-6H-pyrido[1,2-*a*]azepinium Bromide (IX).—The dibromodihydroxy compound (VI, 5.00 g.) was boiled under reflux with acetic anhydride (100 ml.) for 0.75 hr. and the acetic anhydride distilled off under reduced pressure. The dark solid residue (4.24 g., 85%) was purified from ethanol–acetone with the use of charcoal giving 2.34 g. (46%) of an amorphous solid: m.p. 171°, $\lambda_{max}^{H_2O}$ 244 and 317 mμ ($\log_{10}$ ε 4.02 and 4.07), ν_{max}^{Nujol} 1780 (acetyl C=O) and 1165 (C—O) cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{11}Br_2NO_2$: C, 39.92; H, 3.07; N, 3.67. Found: C, 39.7; H, 2.79; N, 3.9.

On heating a small amount of the bromoacetoxy compound for 10 min. with hydrobromic acid on a boiling-water bath, the ultraviolet spectrum of the solution had λ_{max} 253 and 353 mμ. Attempts to isolate a product at this stage gave only oily residues.

10-Acetoxy-7,8-dihydro-6H-pyrido[1,2-*a*]azepinium Bromide (XI).—The cyclic ketone (IV, 0.50 g.) in acetic anhydride (25 ml.) was boiled under reflux for 2 hr., cooled, and then evaporated to dryness. The oily residue was taken up in absolute ethanol, treated with charcoal, and evaporated to small bulk. Careful addition of ethyl acetate precipitated 0.165 g. (24%) of the enol acetate (XI) which was crystallized from ethanol–ethyl acetate as small colorless rhombs: m.p. 158–160°, $\lambda_{max}^{H_2O}$ 242 and 300 mμ ($\log_{10}$ ε 3.88 and 4.07), ν_{max}^{Nujol} 1760 (acetyl C=O) and 1210 (CO) cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{14}BrNO_2$: C, 50.71; H, 4.96. Found: C, 51.00; H, 4.93.

7,9-Dibromo-10-hydroxy-6H-pyrido[1,2-*a*]azepinium Bromide (XII).—The crude bromoacetoxy compound (IX, 4.0 g.) in 50% aqueous hydrobromic acid (80 ml.) was heated on a boiling-water bath for 1 hr. and cooled. To the stirred solution was added bromine (6 g.) in hydrobromic acid (20 ml.). During the addition a yellow perbromide separated. The mixture was heated on a water bath for 0.25 hr. and then evaporated to dryness under reduced pressure. The residue was taken up in water and re-evaporated. Several repetitions of this process gave a solid which was suspended in ethyl acetate and filtered. The crude material was recrystallized from ethanol (charcoal) as yellow-green rhombs, m.p. 183–185° (1.72 g., 45%). Ultraviolet spectra are given in Table I. The compound XII gave a deep jade-green color with neutral aqueous ferric chloride solution.

Anal. Calcd. for $C_{10}H_8Br_3NO$: C, 30.17; H, 2.04; N, 3.52. Found: C, 30.22; H, 2.49; N, 3.44.

7,9-Dibromo-10-hydroxypyrido[1,2-*a*]azepine (XIII).—7,9-Dibromo-10-hydroxy-6H-pyrido[1,2-*a*]azepinium bromide (XII, 1.00 g.) was suspended in water (2 ml.) and saturated aqueous sodium carbonate (2 ml.) was added dropwise. Effervescence occurred at first and then a dark oily layer formed. On standing a few minutes at room temperature deep red crystals started to separate. More sodium carbonate solution (1 ml.) was added and the mixture was left to stand for 0.5 hr. The solution was filtered and the crystals were washed with a few drops of ice-cold water to yield 0.625 g. (79%) of the azepine (XIII). The compound showed no definite melting point and decomposed quickly at temperatures above 100°. Attempts at recrystallization from a variety of solvents led to some decomposition. The analysis specimen was dried under high vacuum for 24 hr. at room temperature. Ultraviolet and visible spectra are given in Table I.

Anal. Calcd. for $C_{10}H_7Br_2NO$: C, 37.87; H, 2.23; N, 4.42. Found: C, 37.37; H, 2.53; N, 4.69.

When the azepine was treated with dilute hydrobromic acid and the solution was evaporated to dryness under reduced pressure, 7,9-dibromo-10-hydroxy-6H-pyrido[1,2-*a*]azepinium bromide (XII) was isolated in good yield, and had identical infrared spectrum and melting point with specimens prepared as described above.

10-Hydroxy-7,8,9,10-tetrahydro-6H-pyrido[1,2-*a*]azepinium Bromide (XV). A.—7,9-Dibromo-10-hydroxy-6H-pyrido[1,2-*a*]-azepinium bromide (XII) (0.50 g.) in 95% ethanol (100 ml.)

was hydrogenated at atmospheric temperature and pressure using 10% palladium-on-charcoal catalyst (0.3 g.). The absorption was equivalent to 4 molar equiv. of hydrogen. The solution was filtered and evaporated. Cooling gave crystals of the alcohol bromide (XV) which were suspended in ethyl acetate and filtered to yield 0.225 g. (74%). Crystallization from ethanol–ethyl acetate gave rhombs: m.p. 172–173.5°, $\lambda_{max}^{H_2O}$ 268 mμ ($\log_{10}$ ε 3.79), ν_{max}^{Nujol} 3250 (OH) cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{14}BrNO$: C, 49.19; H, 5.77; N, 5.72. Found: C, 49.30; H, 5.75; N, 5.74.

B.—The cyclic ketone (IV, 1.00 g.) in 95% ethanol (100 ml.) was hydrogenated using 10% palladium-on-charcoal catalyst (0.5 g.). One molar equivalent of hydrogen was absorbed. Working up as above gave the 10-hydroxy compound (XV) (0.80 g., 80%), m.p. 171°. The spectra were identical with those of the compound prepared from the reduction (A).

C.—9-Bromo-10-acetoxy-6H-pyrido[1,2-*a*]azepinium bromide (IX, 0.40 g.) in 95% ethanol (100 ml.) was hydrogenated with the use of 10% palladium-on-charcoal catalyst (0.3 g.). An uptake of 3 molar equiv. of hydrogen was noted. After filtration and evaporation a solid was isolated by careful addition of ethyl acetate. The infrared spectrum showed it to be the hydroxy compound (XV).

Reduction of the Pyrido[1,2-*a*]azepine (XIII). **A.**—7,9-Dibromo-10-hydroxypyrido[1,2-*a*]azepine (XIII, 0.490 g.) and 10% palladium-on-charcoal catalyst (0.3 g.) in 95% ethanol (40 ml.) containing 40% aqueous sodium hydroxide (0.5 ml.) was hydrogenated. Uptake of hydrogen was slow and after 24 and 48 hr. further 0.15-g. portions of catalyst were added. The total uptake of hydrogen was 3 molar equiv. after which absorption ceased (4 days). The solution was filtered and evaporated to dryness and the residue was triturated with chloroform. The chloroform mixture was filtered from contaminating inorganic material and evaporated. The oil remaining was distilled in a bulb tube at a bath temperature of 125–165° (0.001 mm.): $\lambda_{max}^{95\%\ EtOH}$ 257, 262, and 268 mμ ($\log_{10}$ ε 3.46, 3.51, and 3.40); $\nu_{max}^{liq\ film}$ 3400 (OH), 1120, 1060, and 1000 (acetal C—O) cm.$^{-1}$. The liquid was identical with the acetal (XVI) described below.

Anal. Calcd. for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15; N, 5.53. Found: C, 66.67; H, 8.65; N, 5.64.

B.—The azepine (0.60 g.) in 95% ethanol (30 ml.) together with sodium acetate trihydrate (0.60 g.) and 10% palladium-on-charcoal catalyst (0.35 g.) was hydrogenated. Four molar equivalents of hydrogen were absorbed before uptake of hydrogen ceased. The solution was filtered and evaporated. The residue was suspended in a 1:1 ethanol–ethyl acetate mixture and the inorganic material was filtered off. The filtrate was evaporated and again treated with ethanol–ethyl acetate. Again the filtrate was evaporated and the residue was triturated with ether. Filtration gave a solid which was identified as 10-hydroxy-7,8,9,10-tetrahydro-6H-pyrido[1,2-*a*]azepinium bromide (XV) by its infrared spectrum. The filtrate when evaporated gave an oil which was found by gas chromatography to consist of two main components in approximately equal amounts. Separation and identification of these was not attempted.

5-Hydroxy-5-(2′-pyridyl)pentanal Diethyl Acetal (XVI).—4-Chloro-1-butyraldehyde diethyl acetal (15 g.) prepared by the method of Loftfield[8] was slowly added under an atmosphere of nitrogen to a hot, stirred solution of tetrahydrofuran (100 ml.) and magnesium (3 g.). The mixture was boiled under reflux for 3 hr. after the addition, cooled, and then slowly added to a stirred solution of redistilled pyridine-2-aldehyde (7.5 g.) in tetrahydrofuran (50 ml.) under a nitrogen atmosphere. The mixture was boiled under reflux for 0.5 hr. and after cooling was hydrolyzed with a solution of ammonium chloride in ammonia (s.g. 0.88). The organic layer was separated and the aqueous layer was extracted with ether. The combined organic extracts were dried (sodium sulfate) and the ether and tetrahydrofuran were distilled off. Distillation of the residue under reduced pressure gave 7.35 g. (41%) of the acetal (XVI), b.p. 134–140° (0.15 mm.). Redistillation gave 6.5 g. (36%), b.p. 128° (0.08 mm.). The acetal (XVI) had the same ultraviolet and infrared spectra as the product from hydrogenation (A) of the azepine.

Anal. Calcd. for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15; N, 5.53. Found: C, 66.53; H, 9.28; N, 5.80.

2-(2′-Pyridyl)-6-hydroxytetrahydropyran (XVIII).—The hydroxy acetal (XVI, 1.5 g.) in 2 *N* hydrochloric acid (7.5 ml.) was shaken for 1 hr. and then basified with solid sodium carbonate. The basified solution was extracted with ether; the ether extracts were dried and distilled giving 1.00 g. of a colorless oil. This was distilled at 108–111° (0.2 mm.) to give 0.55 g. (52%) of the pyran (XVIII): $\lambda_{max}^{95\%\ EtOH}$ 257, 262, and 268 mμ, ($\log_{10}$ ε 3.62, 3.57, and 3.44); $\nu_{max}^{liq\ film}$ 3350 (OH) cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.01; H, 7.31. Found: C, 66.53; H, 7.40.

The n.m.r. spectrum of the compound in carbon tetrachloride showed the following peaks: doublet centered at 8.33, weight of 1 (C-6-H of pyridine); multiplet centered at 7.2, weight of 3 (C-3, -4, and -5 of pyridine); multiplet centered at 4.85, weight of 3 (C-2–H, C-6–H of pyran and hydroxyl proton); multiplet centered at 1.84 p.p.m., weight of 6 (methylene groups of pyran ring).

Reaction of 7,9-Dibromo-10-hydroxypyrido[1,2-*a*]azepine (XIII) and Tetracyanoethylene.—The azepine (0.20 g., as isolated, not subjected to intensive drying) was dissolved in chloroform (25 ml.) and tetracyanoethylene (0.082 g.) dissolved in a 1:1 chloroform–ethyl acetate mixture (10 ml.) added. A vivid blue color was produced immediately and this faded on standing with the concomitant precipitation of a dark brown solid. Filtration gave 0.183 g. (60%) of a 1:1 adduct which had no definite melting point but which decomposed on heating: ν_{max}^{KBr} 2180 (C≡N) cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_7Br_2N_5O \cdot 2H_2O$: C, 39.96; H, 2.30. Found: C, 40.46; H, 2.25.

10-Oximino-7,8,9,10-tetrahydro-6H-pyrido[1,2-*a*]azepinium Bromide (XX).—Hot ethanolic solutions of crystalline sodium acetate (2.3 g.) and hydroxylamine hydrochloride (2.3 g.) were mixed and cooled and the precipitated sodium chloride was filtered off. The cyclic ketone (IV) (2.3 g.) was then added to the solution and the mixture was boiled under reflux for 0.75 hr. The solution was then evaporated to small bulk and cooled, and the crystalline product was filtered. Passage of this in 95% ethanolic solution through an Amberlite IRA 400 (Br) column followed by evaporation and filtration gave 1.75 g. (75%) of the oxime bromide (XX). Recrystallization from ethanol gave colorless needles: m.p. 275–278°, $\lambda_{max}^{H_2O}$ 284 mμ ($\log_{10}$ ε 3.96).

Anal. Calcd. for $C_{10}H_{13}BrN_2O$: C, 46.71; H, 5.10; N, 10.89. Found: C, 46.47; H, 5.09; N, 11.02.

(8) R. B. Loftfield, *J. Am. Chem. Soc.*, **73**, 1365 (1951).