Anal. Calcd. for $C_{19}H_{24}ClNO$: Cl, 11.20. Found: Cl, 11.75, 11.77.

1-Benzyl-4-piperidyl phenyl ketone hydrobromide. A solution of 17 g. of 1-benzyl-4-piperidylphenylcarbinol hydrochloride and 4.1 g. of chromic acid in 200 ml. of acetic acid was heated on the steam bath for 1 hr. The solvent was removed by distillation under reduced pressure, and the residue was dissolved in chloroform. The solution was saturated with anhydrous hydrogen bromide, and the chloroform was removed by evaporation. The residue was recrystallized from isopropyl alcohol to give 12 g. (77%) of 1-benzyl-4-piperidyl phenyl ketone hydrobromide, m.p. 235–238°.

Anal. Calcd. for $C_{19}H_{23}BrNO$: Br, 22.18. Found: Br, 22.05.

1-Benzyl-4-bromo-4-piperidyl phenyl ketone hydrobromide. A suspension of 12 g. of 1-benzyl-4-piperidyl phenyl ketone hydrobromide in chloroform was treated with 2.5 ml. of bromine, and the mixture was allowed to stand overnight. The solvent was removed by distillation, and the residue was dissolved in methanol. Phenol was added to remove the perbromide-bromine,[6] and 13 g. (88%) of 1-benzyl-4-bromo-4-piperidyl phenyl ketone hydrobromide, m.p. 162–164°, precipitated as a white solid on addition of ether.

Anal. Calcd. for $C_{19}H_{23}Br_2NO$: 1 Br, 18.20. Found: Br, 18.29.

6-Benzyl-2-methoxy-2-phenyl-1-ox-6-azaspiro[2.5]octane (III). To a solution of 13.5 g. of sodium methoxide in 150 ml. of methanol was added 11 g. of 1-benzyl-4-bromo-4-piperidyl phenyl ketone hydrobromide. The solution was heated under reflux for 4 hr., and the solvent was removed by distillation under reduced pressure. The residue was distilled under reduced pressure to give 6.5 g. of 6-benzyl-2-methoxy-2-phenyl-1-ox-6-azaspiro[2.5]octane (III), b.p. 170–175° at 2 mm., which on treatment with organic acids in ether gave the esters in Table I.

Anal. Calcd. for $C_{20}H_{23}NO_2$: C, 77.63; H, 7.49. Found: C, 77.60, 77.78; H, 7.39, 7.52.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NEW HAMPSHIRE]

Hydrates of 1-Methyl-3- and -4-piperidone Hydrochlorides[1]

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The salts of 1-methyl-4-piperidone and 1-methyl-3-piperidone have been shown to crystallize with one molecule of water from solvents which contain water. The infrared absorption spectra of these hydrates clearly prove that the water is present as the hydrate of the carbonyl group. The preparation of 1-methyl-3-piperidone by a novel synthesis is reported.

The addition of water to the carbonyl group of aldehydes or ketones leads to stable hydrates in only a few cases. Those examples of stable hydrates that are known have in common one or more strongly electron-attracting groups attached to the carbonyl, and this structural feature is considered necessary for a stable hydrate. The formal positive charge of an amine salt, therefore, would be expected to stabilize the hydrate of a carbonyl located in the same molecule. Although stable hydrates of salts of amino-ketones have not been demonstrated, ketals have been reported to be formed by the reaction of 4-piperidone hydrochloride,[3b] 1-alkyl-4-piperidone quaternary salts,[4] and 1-alkyl-4-piperidone hydrochlorides[5] with alcohol. This reaction is promoted by the positive charge in the salt; however, the strain inherent in a tercovalent carbon within a six-membered ring[6] alone appears to provide the driving force for the formation of the ketal. Thus, unlike other ketones which undergo partial reaction with alcohols by addition,[7] cyclohexanone is converted to the ketal.[8] Since 1-methyl-4-piperidone hydrochloride

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(2) Abstracted in part from the Thesis of REA submitted to the Graduate School of the University of New Hampshire in partial fulfillment of the requirements of the degree of Master of Science.

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(I) has both structural features which would be expected to promote the stability of a ketone hydrate, the report by Craig and Tarbell[9] that I crystallized from aqueous solvents with a molecule of water suggested that the ketone hydrate (II) of I was stable and could be isolated. Since hydrates of these amino ketones would be of value in investigating the conformation of piperidines, the structures of the salts of 1-methyl-4- and -3-piperidones were elucidated.

The 1-methyl-4-piperidone hydrochloride (I) used in this investigation[10] was prepared by the method of McElvain and co-workers[3]; however, the previous methods of synthesis of 1-methyl-3-piperidone hydrochloride (III)[11] are complex due to the necessity of preparing an unsymmetrical amino diester for the Dieckmann cyclization, the conventional procedure for preparing piperidones. The selective reduction of pyridinium salts to tetrahydropyridines by sodium borohydride[12] suggested a shorter route to 1-methyl-3-piperidone (VI). 3-Hydroxypyridine (VII), available commercially,[13] was alkylated simultaneously on nitrogen and oxygen with methyl iodide, and, without isolation, the pyridinium salt was reduced with sodium borohydride to 1-methyl-1,2,5,6-tetrahydro-3-pyridyl methyl ether (VIII). On hydrolysis with hydrobromic acid, VIII gave 1-methyl-3-piperidone hydrobromide (IX).

This procedure also was evaluated as a method of synthesis of 1-methyl-4-piperidone (V). The conversion of 4-nitropyridine-1-oxide (X) to 4-benzyloxypyridine (XI) was accomplished by known procedures,[14] and the methiodide of XI was reduced to 1-methyl-1,2,3,6-tetrahydro-4-pyridyl benzyl ether (XII), which on hydrolysis with hydrochloric acid gave 1-methyl-4-piperidone hydrochloride hydrate (II). This method, however, was not superior to that of McElvain.[3]

The piperidone hydrochlorides (II and IV) each gave two melting points when determined on a Fisher hot stage apparatus. The lower temperature corresponded to that observed in a capillary. These results in conjunction with the halogen analyses showed that 1-methyl-3-piperidone hydrochloride (IV), as well as II, was a hydrate.

The structure determination of the hydrates II and IV was accomplished by a study of the infrared absorption spectra of these compounds in the solid state as mulls in Halocarbon[15] (1300–4000 cm.$^{-1}$) and Nujol (650–1300 cm.$^{-1}$). While the spectra of the amines V and VI, as liquid films, showed strong absorption at 1715–1716 cm.$^{-1}$ characteristic of carbon to oxygen double bond stretching, and no absorption above 3100 cm.$^{-1}$, the spectra of the hydrochlorides II and IV showed no absorption between 1500 and 2000 cm.$^{-1}$ The spectra of II and IV had large, broad bands at about 3300 cm.$^{-1}$ in addition to the broad N—H band of the salt at about 2700 cm.$^{-1}$ The spectrum of IV contained a small band at 2827 cm.$^{-1}$ not found in the spectrum of II.

The analyses and the infrared spectra require that II and IV, molecular formula $C_6H_{14}ClNO_2$, have no free carbonyl group but contain hydroxyl functions. These requirements are compatible with the hydrate structures II and IV, but do not eliminate the possibility of an hydrated enol of I and III or a hydrated product of transannular interaction between the nitrogen and the carbonyl. The possibility of an enol was removed by failure of II and IV to give a reaction with ferric chloride and the absence of absorption in the infrared spectrum characteristic of carbon to carbon double bond. The second possibility was unlikely in view of Leonard's results with related compounds,[16] and such interaction would be impossible with the quaternary salts of 1-methyl-3- and -4-piperidone

(9) L. E. Craig and D. S. Tarbell, *J. Am. Chem. Soc.*, **71**, 465 (1949).

(10) The authors wish to express appreciation to Eli Lilly and Co. for a generous sample of 1-methyl-4-piperidone hydrochloride and to Dr. Edwin R. Shepard of that company through whose assistance the compound was obtained.

(11) E. A. Prill and S. M. McElvain, *J. Am. Chem. Soc.*, **55**, 1233 (1933); S. M. McElvain and J. F. Vozza, *J. Am. Chem. Soc.*, **71**, 896 (1949); and N. J. Leonard and E. Barthel, *J. Am. Chem. Soc.*, **72**, 3632 (1950).

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(13) The authors wish to express appreciation to Nepera Chemical Company, Yonkers 2, N. Y., for a sample of 3-hydroxypyridine used in this study.

(14) E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953).

(15) Halocarbon Products Corp., 2012 88th St., North Bergen N. J. See D. S. Crocket and H. M. Haendler, *Anal. Chem.*, in press.

(16) N. J. Leonard, R. C. Fox, and M. Oki, *J. Am. Chem. Soc.*, **76**, 5708 (1954).

(V and VI). The methiodides XIII and XIV, however, were similar in properties to II and IV. Thus, the hydrates of 1-methyl-3- and -4-piperidone hydrochlorides must be represented by the *gem*-diols II and IV. The protection of the carbonyl group of 1-methyl-3-piperidone hydrochloride (III) by the formation of the hydrate (IV) would explain the greater stability to air of the hydrochloride as compared to the base (VI).

The double melting points of II and IV determined on a hot stage led to the attempted preparation of the anhydrous hydrochlorides I and III by sublimation of the hydrates. This technique gave I having a melting point corresponding to that reported by Craig and Tarbell.[9] The infrared absorption spectrum of I as a solid mull gave a very small band at 3300 cm.$^{-1}$ but a strong broad band at 1733 cm.$^{-1}$ This shift of 18 cm.$^{-1}$ of the carbonyl stretching frequency on formation of the salt is a result of the repression of delocalization of the *pi* electrons of the carbonyl group due to the proximity of the formal charge on the nitrogen. The absorption of the N—H bond of the salt was altered also. The structure of the band was very complex and was shifted to lower frequencies (*ca.* 2500 cm.$^{-1}$). This change also reflects the interaction of the carbonyl function and the positive nitrogen.

The anhydrous hydrochloride (III) of 1-methyl-3-piperidone did not appear as the sublimate but could be formed by heating the hydrate IV under reduced pressure. The halogen analysis of III corresponded to the anhydrous hydrochloride, and the infrared absorption spectrum also supported this structure. The spectrum showed strong absorption at 1725 cm.$^{-1}$, indicating a free carbonyl, and the N—H absorption band was complex and shifted to about 2470 cm.$^{-1}$. These changes are closely related to those observed with I and II.

The methobromides of 1-methyl-3- and -4-piperidones behaved similarly to the hydrochlorides. The salts, XIII and XIV, were prepared in anhydrous ether, and the analyses and infrared absorption spectra indicated only traces of the hydrates. The carbonyl stretching frequencies were 1723 (XIII) and 1729 (XIV) cm.$^{-1}$. Recrystallization of the methobromides from water-acetone gave the corresponding hydrates. The infrared spectrum of 1-methyl-4-piperidone methobromide hydrate (XIIIa) gave an hydroxyl band at 3360 cm.$^{-1}$ and a weak band at 1723 cm.$^{-1}$. The spectrum of 1-methyl-3-piperidone methobromide hydrate (XIVa) indicated the presence of the hydroxyl groups by absorption at 3080 and 3300 cm.$^{-1}$. The melting points of the hydrates XIIIa and XIVa were identical with anhydrous salts XIII and XIV unless the hydrates were introduced into a bath at 150° in which case they both melted completely.

This study proved that the salts of 1-methyl-3- and -4-piperidones form stable hydrates of the carbonyl, and that the isolation of the anhydrous forms of the hydrochlorides is difficult. Thus it is evident that there is the possibility that the salt of any amino ketone may add readily the elements of water necessitating a careful examination of any amino ketone salt.

EXPERIMENTAL

Infrared absorption spectra. The infrared absorption spectra were determined using a Perkin-Elmer, Model 21, infrared spectrophotometer, with sodium chloride optics. The spectra of solids were determined as mulls in series 11–14 Halocarbon oil[15] from 1300 to 4000 cm.$^{-1}$ and in Nujol from 650 to 1300 cm.$^{-1}$

1-Methyl-4-piperidone hydrochloride hydrate (II). The material used in this investigation was prepared by the method of McElvain and co-workers.[8]

4-Benzyloxypyridine (XI). A solution of 1 g. of 4-benzyloxypyridine-1-oxide[14] in 15 ml. of cold chloroform was treated with 1.9 ml. of phosphorus trichloride. The solution was heated at 70–80° for 1 hr., cooled, and diluted with 15 ml. of water. The mixture was neutralized with sodium hydroxide, and the layers were separated. The aqueous layer was extracted three times with chloroform, and the combined chloroform layers were dried over anhydrous potassium carbonate. Fractional distillation of the solution gave 0.45 g. (49%) of 4-benzyloxypyridine (XI), b.p. 193–196°/20 mm., m.p. 49–52°; lit.[17] b.p. 155–160°/4 mm., m.p. 55–56°. The methiodide of 4-benzyloxypyridine (XI) was prepared in acetone and melted at 148–151°.

1-Methyl-1,2,3,6-tetrahydro-4-pyridylbenzyl ether (XII). A solution of 5.29 g. of 4-benzyloxypyridine methiodide in 50 ml. of methanol was treated with 1.5 g. of sodium borohydride. The solvent (31 ml.) was removed by distillation, and water was added to the residue. Anhydrous potassium carbonate was added, and the aqueous solution was extracted with four portions of ether. After drying over potassium carbonate, the ether solution was concentrated, and the residue was distilled under reduced pressure to give 2.81 g. (86.4%) of 1-methyl-1,2,3,6-tetrahydro-4-pyridylbenzyl ether (XII), b.p. 170–175/17 mm., n_D^{22} 1.5399.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.80; H, 8.43. Found: C, 76.49; H, 8.53.

1-Methyl-4-piperidone (V). A solution of 2.31 g. of XII in 10 ml. of concentrated hydrochloric acid and 4 ml. of water was heated under reflux for 4 hr. On cooling, the solution was extracted with ether to remove the benzyl alcohol, and the remaining acidic solution was neutralized with potassium carbonate and extracted with ether. The ether extract was dried and fractionally distilled to give 0.92 g. (71.5%) of 1-methyl-4-piperidone (V), b.p. 68–71°/17 mm., n_D^{23} 1.4556; lit.[8] b.p. 63–65°/18 mm. n_D^{25} 1.4581.

1-Methyl-4-piperidone hydrochloride hydrate (II). A solution of 1-methyl-4-piperidone in dilute hydrochloric acid was evaporated under reduced pressure. The residue crystallized on washing with acetone to give II, m.p. 88–91° in a capillary. On a hot stage the solid melted at 88–91°, resolidified, and melted at 157–163°.

Anal. Calcd. for $C_6H_{14}ClNO_2$: Cl, 21.15. Found: 21.10, 21.02.

Anhydrous 1-methyl-4-piperidone hydrochloride (I). A sample of II was sublimed under a pressure of 2 mm. at 120°. The sublimate melted at 165–168°, lit.[9] m.p. 164–167°.

Anal. Calcd. for $C_6H_{12}ClNO$: Cl, 23.70. Found: Cl, 23.70, 23.77.

Anhydrous 1-methyl-4-piperidone methobromide (XIII). A solution of 2.0 g. of 1-methyl-4-piperidone (V) in ether was saturated with methyl bromide. The precipitate which formed was removed by filtration to give 1.7 g. of 1-methyl-4-piperidone methobromide (XIII), m.p. 187–190°.

(17) E. Shaw, *J. Am. Chem. Soc.*, **71**, 68 (1949).

Anal. Calcd. for $C_7H_{14}BrNO$: Br, 38.41. Found: 38.17, 38.11.

1-Methyl-4-piperidone methobromide hydrate (XIIIa). The methobromide (XIII) was dissolved in water and precipitated by addition of acetone. The resulting solid melted when introduced into a bath at 150°.

Anal. Calcd. for $C_7H_{16}BrNO_2$: Br, 35.34. Found: Br, 35.29, 35.30.

1-Methyl-1,2,5,6-tetrahydro-3-pyridyl methyl ether (VIII). A solution of 32 g. of 3-hydroxypyridine (VII) and 21 g. of sodium methoxide in 150 ml. of methanol was treated with 100 g. of methyl iodide. The mixture was heated under reflux for 7 hr., cooled, and 26 g. of sodium borohydride was added portionwise. The solvent was removed by distillation, and water was added to the residue. Potassium carbonate was added to the aqueous solution, and ether was used for extraction. After drying over potassium carbonate, the ether solution was concentrated, and the residual oil was distilled under reduced pressure to give 12.93 g. (40%) of 1-methyl-1,2,5,6-tetrahydro-3-pyridyl methyl ether (VIII), b.p. 60–63°/11 mm., n_D^{24} 1.4663.

Anal. Calcd. for $C_7H_{13}NO$: C, 66.09; H, 10.30. Found: C, 66.13; H, 10.63.

The *picrate* was prepared in ethanol, m.p. 119–120°. The molecular weight determined by the ultraviolet absorption method[18] was 354; the calculated value is 356.

Anal. Calcd. for $C_{13}H_{16}N_4O_8$: C, 43.82; H, 4.53, Found: C, 44.19; H, 4.48.

1-Methyl-3-piperidone (VI). A solution of 12.9 g. of VIII in 40 ml. of 48% hydrobromic acid was heated under reflux for 6 hr. The solution was neutralized and extracted with ether. The ether solution was concentrated, and the residue was distilled under reduced pressure to give 10.7 g. of 1-methyl-3-piperidone (VI), b.p. 65–70°/15 mm., n_D^{26} 1.4535; lit.[11] b.p. 63–64°/13 mm., n_D^{25} 1.4559. Addition of anhydrous hydrogen chloride to a solution of the 1-methyl-3-piperidone in ether gave 12.00 g. of 1-methyl-3-piperidone hydrochloride hydrate, m.p. 105–108°; lit.[11] m.p. 110–111°.

Anal. Calcd. for $C_6H_{14}ClNO_2$: Cl, 21.15; Found: Cl, 21.19, 21.02.

1-Methyl-3-piperidone hydrobromide (IX). A solution of 10.8 g. of VIII in 33 ml. of hydrobromic acid was heated under reflux for 8 hr. and evaporated to dryness under reduced pressure to give an oily residue which crystallized on treatment with acetone. The solid was isolated by filtration to give 15.9 g. of IX, m.p. 103–106°.

Anal. Calcd. for $C_6H_{12}BrNO$: Br, 41.18. Calcd. for $C_6H_{14}BrNO_2$: Br, 37.68. Found: Br, 38.02, 37.99.

Anhydrous 1-methyl-3-piperidone hydrochloride (III). A sample of the hydrate IV was heated under reduced pressure. The residue, III, melted at 138–141°.

Anal. Calcd. for $C_6H_{12}ClNO$: Cl, 23.70. Found: 23.39.

Anhydrous 1-methyl-3-piperidone methobromide (XIV). A solution of 1-methyl-3-piperidone (VI) and methyl bromide in ether deposited the methobromide (XIV) m.p. 175–179°, on standing.

Anal. Calcd. for $C_7H_{14}BrNO$: Br, 38.41. Found: Br, 37.97, 38.14.

1-methyl-3-piperidone methobromide hydrate (XIVa). A solution of the salt XIV was treated with acetone to precipitate 1-methyl-3-piperidone methobromide hydrate (XIVa) which melted on introduction into a bath at 150°.

Anal. Calcd. for $C_7H_{16}BrNO_2$: Br, 35.34. Found: Br, 35.29.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BROOKLYN COLLEGE]

Synthesis of 2,6-Disubstituted Pyrazines and Related Derivatives

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A number of 2,6-disubstituted pyrazines and related derivatives have been prepared. A new procedure for the preparation of 7-methyllumazine is described. 7-Methyllumazine has been cleaved to furnish both 6-methyl-2-pyrazinol and 2-amino-6-pyrazinol was coupled to furnish a new series of azopyrazine dyes. These azopyrazine dyes were reduced in acid solution to furnish 5-amino-6-methyl 2-pyrazinols.

7-Methyllumazine (2,4-dihydroxypyrimido-4,5-6-pyrazine) (I) is readily cleaved by alkali.[1] The products are 2-amino-6-methyl-3-pyrazinoic acid (II) and 2-hydroxy-6-methyl-3-pyrazinoic acid (III). These carboxylic acids are readily decarboxylated to the 2-amino- (IV) and the 2-hydroxypyrazines (XII). The conventional approach to lumazine synthesis involving the condensation of a 4,5-diaminopyrimidine with an α,β-dicarbonyl compound[2,3] gives brown gelatinous products. A fine, yellow, crystalline 7-methyllumazine is obtained here by condensation in acid solution of 5,6-diaminouracil with stabilized methylglyoxal (30% solution).[4] This procedure furnished practically quantitative yields of micro crystalline 7-methyllumazine and also permitted quantitative detection of α-dicarbonyl compounds in quantities as low as 5 γ per ml. equivalent to 2 γ of methyl glyoxal.[5]

Owing to the paucity of 2,6-disubstituted pyrozines, it was of interest to investigate further the preparation of compounds of this class. In approaching this problem, the method of Weijlard and coworkers for the conversion of 7-methyllumazine into 2-amino-6-methylpyrazine (IV) was used. Efforts to prepare 2,6-diaminopyrazine through a

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(4) Methyl glyoxal 930% stabilized solution was obtained from Carbide and Carbon Chemicals Co. 30 2. 42nd St., New York, N. Y.

(5) L. Sattler and F. W. Zerban, *Ind. Eng. Chem.*, **41**, 1401 (1949).