New Routes to Systems with Bridgehead Nitrogen. Cyclization Reactions of the Hydroxyacetylpiperidines and Derivatives (1)

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Reactions of the hydroxyacetylpiperidines, their ethylene ketals, and the *N*-benzyl derivatives of these new piperidines (2) have been examined. New cyclization reactions leading to bridgehead nitrogen compounds are described in this report. As observed in previous investigations, *N*-benzyl substitution in the piperidines facilitates cyclization(3-5).

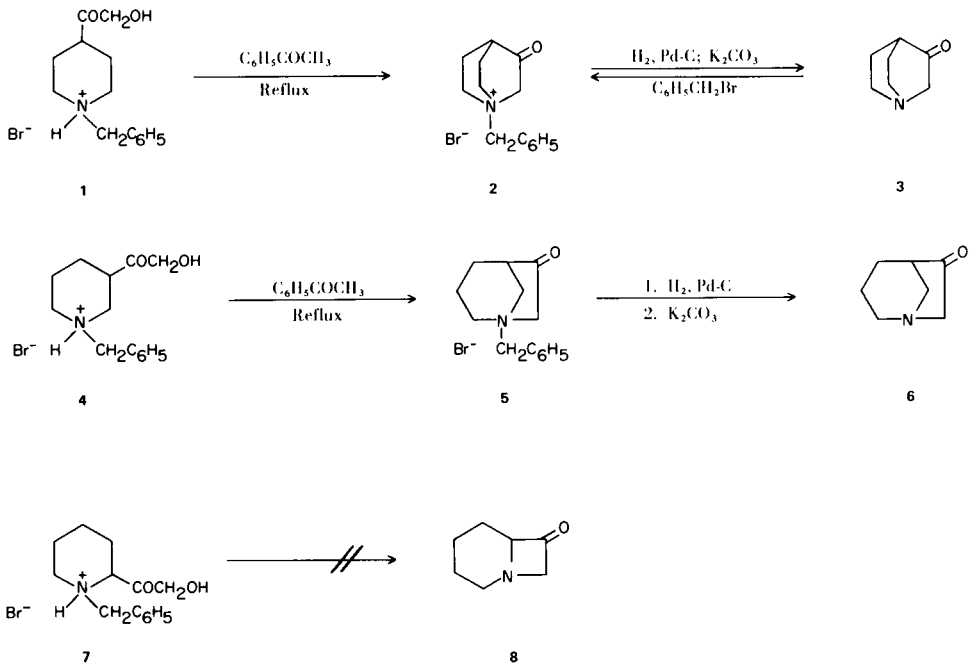
N-Benzyl-4-(hydroxyacetyl)piperidine hydrobromide (1) (2) cyclodehydrates in refluxing acetophenone solvent to produce 1-benzyl-3-quinuclidinone bromide (**2**). Debenzylation of **2** occurs readily by hydrogenation with palladium-charcoal catalyst in ethanol. The product, 3-quinuclidinone hydrobromide, was converted to 3-quinuclidinone (**3**), isolated as its picrate derivative (Scheme I).

Similarly, *N*-benzyl-3-(hydroxyacetyl)piperidine hydrobromide (**4**) leads to *N*-benzyl-1-azabicyclo[3.2.1]octan-6-one bromide (**5**). Debenzylation of **5** by hydrogenation led to 1-azabicyclo[3.2.1]octan-6-one hydrobromide which was isolated and converted to the free base (**6**, isolated as its picrate). Yields in the cyclodehydration reactions (**1** → **2**, **4** → **5**) are 40-50%, based on infrared analyses of product mixtures. The debenzylations of the *N*-benzyl bromides (**2**,**5**) to the 1-azabicycloöctanones (**3**,**6**) proceed in 80-90% yields. Heating *N*-benzyl-2-(hydroxyacetyl)-piperidine hydrobromide (**7**) in refluxing acetophenone or other solvents, followed by hydrogenation, failed to produce 1-azabicyclo[4.2.0]octan-7-one (**8**). The cyclization reactions leading to **2** and **5** could be realized in low conversions in other solvents (*e.g.*, 5-7% in refluxing benzonitrile or anisole).

Heating dilute solutions of the unbenzylated hydroxyacetylpiperidine cations (chloride, bromide, bisulfate or tosylate anions) in various solvents gave traces of 1-azabicycloöctanones. Polymeric material and/or recovered reactant resulted. The hydroxyacetylpiperidine cations in refluxing aqueous solution are rather stable.

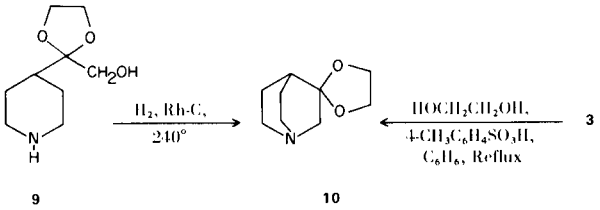
Heating dilute solutions of the free hydroxyacetylpiperidine bases in various solvents usually results in dehy-

SCHEME I



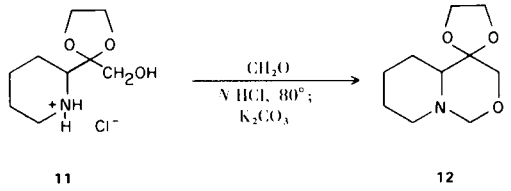
dration with formation of insoluble polymers (2). In refluxing diglyme 4-hydroxyacetylpiperidine gave a low conversion to 3-quinuclidinone and much polymer.

2-Hydroxymethyl-2-(4-piperidyl)-1,3-dioxolane (**9**) on heating with rhodium-charcoal catalyst and hydrogen at 240° produced 3-quinuclidinone ethylene ketal (**10**), 4% conversion. This ketal was also prepared in 80% yield from 3-quinuclidinone (**3**) by reaction with ethylene glycol and *p*-toluenesulfonic acid in refluxing benzene. Other reaction conditions involving heating ketal **9** at



various temperatures and pressures with various platinum metal and certain metal oxide catalysts, with and without solvents and/or hydrogen, failed to effect cyclization to **10**. Similarly, 2-hydroxymethyl-2-(2- and 3-piperidyl)-1,3-dioxolanes failed to undergo cyclization to 1-azabicycloöctanone ketals. Reactant ketals were often recovered in these experiments.

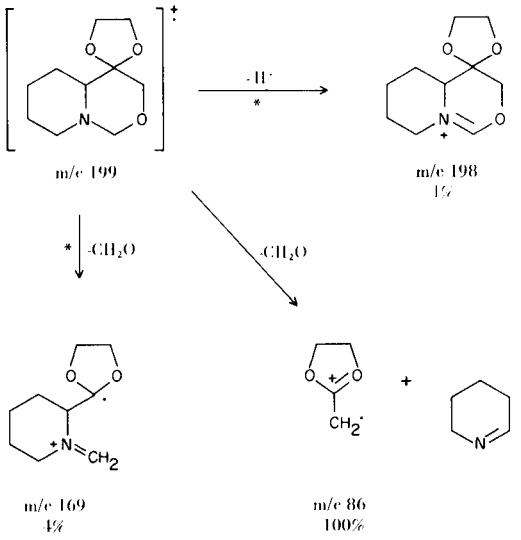
2-Hydroxymethyl-2-(2-piperidyl)-1,3-dioxolane hydrochloride (**11**) reacts with formaldehyde in *N* hydrochloric acid (80°, 15 hours) to produce the 3-oxaquinolizidin-1-one ketal **12**, 86% yield. This reaction has been applied



previously to various substituted 2-(2-piperidyl)ethanols, but not to those having ketal groups (6). Ketal **12** is very resistant to acid hydrolysis and the corresponding ketone could not be prepared; vigorous reaction conditions resulted in extensive decomposition and some recovery of the reactant.

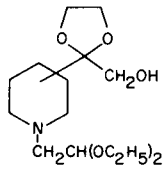
Structure **12** is supported by its ir, nmr, and mass spectra (see Experimental and Scheme II). A metastable peak at 197 indicates loss of hydrogen radical from the molecular ion (M*, m/e 199). Formaldehyde is lost with formation of a fragment m/e 169 (metastable peak at 143.6; calcd. 143.5). The principal fragment obtained (m/e 86), characteristic of ethylene ketals (7), is believed to form from the molecular ion by loss of formaldehyde and a tetrahydropyridine. A relatively less abundant fragment, m/e 83, also appears in the mass spectrum suggesting formation of a tetrahydropyridyl radical cation.

SCHEME II



2-Hydroxymethyl-2-(3- and 4-piperidyl)-1,3-dioxolanes, in contrast to the 2-piperidyl isomer, are readily hydrolyzed to their parent ketones in acid media. In hot *N* hydrochloric acid with formaldehyde they produce polymeric material or the hydroxymethylpiperidines after treatment with saturated potassium carbonate solution.

Reaction of 2-hydroxymethyl-2-(3- and 4-piperidyl)-1,3-dioxolanes with bromoacetaldehyde diethylacetal and sodium carbonate in refluxing ethanol (15-20 hours) led to 95-100% yields of the oily *N*-2,2-diethoxyethyl derivatives **13,14** (undistilled) (3). The corresponding 2-piperidyl derivative could not be prepared by this procedure and reactant was recovered. Heating **13** or **14** in refluxing *N* hydrochloric acid led to polymeric material and no bridgehead nitrogen compounds could be isolated.



13, 3-piperidyl
14, 4-piperidyl

EXPERIMENTAL (8)

1-Benzyl-3-quinuclidinone Bromide (2).

A solution of 1.25 g. (0.01 mole) of 3-quinuclidinone (**3**) in 15 ml. of 2-propanol was treated with 1.9 g. (0.011 mole) of benzyl bromide. An exothermic reaction occurred and the quaternary salt precipitated immediately. The mixture was allowed to

stand at room temperature for 18 hours, then warmed on the steam bath for 5 hours. After chilling to 0° the mixture was filtered and the precipitate washed with cold 2-propanol to yield 2.70 g. (91%) of pure **2**, m.p. 239-240°; recrystallization from 2-propanol gave flat prisms, m.p. 238-239°; ν (potassium bromide), 1750 cm^{-1} (C=O); lit. (5) m.p. 233-236°.

Anal. Calcd. for $C_{14}H_{18}BrNO$: C, 56.76; H, 6.12; Br, 26.98; N, 4.73. Found: C, 57.03; H, 6.19; Br, 27.00; N, 4.71.

3-Quinuclidinone (**3**).

A. From 1-Benzyl-3-quinuclidinone Bromide (**2**).

A solution of 0.50 g. of 1-benzyl-3-quinuclidinone bromide (**2**) in 30 ml. of 50% aqueous ethanol and 0.2 g. of 10% palladium on charcoal catalyst was shaken with hydrogen in a Parr apparatus (51 psi, 25°) for 35 minutes. The mixture was filtered and concentrated to remove ethanol. The residue was treated with potassium carbonate to liberate the base which was extracted with methylene chloride. After drying, the extracts were concentrated to yield 0.18 g. (85%) of crude 3-quinuclidinone, m.p. 128-148°. This material was treated with aqueous ethanolic picric acid to yield 0.35 g. (60% yield from **2**) of pure 3-quinuclidinone picrate, m.p. 212-215°, lit. (9) m.p. 210°.

B. From 1-Benzyl-4-(hydroxyacetyl)piperidine Hydrobromide (**1**).

A 1.0-g. sample of hydrobromide **1** (2) and 75 ml. of acetophenone were heated under reflux for 3 hours. Water (0.05 ml.) was removed in a Dean-Stark trap. After cooling, the solution was filtered to remove 0.15 g. of unreacted **1** and the filtrate concentrated to yield an oily product having strong infrared bands of equal intensity at 1750 and 1720 cm^{-1}. The precipitate was crystallized from 2-propanol to yield crystals of crude **2** having strong carbonyl absorption at 1750 cm^{-1} and weak absorption at 1720 cm^{-1}, indicating a mixture of **2** and **1**. From the intensity of the absorption band at 1750 cm^{-1} in the product the yield of 3-quinuclidinone cyclization product in this and other runs is estimated to be 40-50%. Addition of hydrogen bromide, sodium bromide or lithium bromide improved conversions somewhat, but resulted in some self-condensation of the acetophenone solvent to produce dypnone. The crude cyclization product was used without purification for conversion to 3-quinuclidinone.

The crude, unrecrystallized cyclization product from a parallel 1.0-g. run was treated with ether and the mixture extracted with four 25-ml. portions of water. The combined water extracts were extracted once with ether. Hydrogenation of the aqueous solution in a Parr apparatus with 1.0 g. of 10% palladium-charcoal catalyst (50 psi, 25°, 30 minutes) was followed by filtration and concentration of the residue to a small volume. Potassium carbonate was added and the mixture extracted with methylene chloride. Concentration of the dried extracts gave crude 3-quinuclidinone which was treated with ethanolic picric acid to produce 3-quinuclidinone picrate, 42 mg., orange prisms, m.p. 214-217°; when mixed with an authentic sample, m.p. 212-214°, the melting point was not depressed.

In parallel experiments the hydrobromide **1** was heated with other solvents in which it is less soluble, including diglyme, acetonitrile, benzonitrile, mesitylene, toluene and anisole. Low conversions (5-7%) to **2** (based on infrared data) were observed in benzonitrile and anisole, much starting material being recovered. No reaction occurred in boiling acetonitrile or toluene. The reaction is quite slow at temperatures below 190°. Decomposition of the solvent occurred rapidly when **1** was heated under reflux in dimethylsulfoxide. No conversion to a 3-quinuclidinone derivative was observed when **1** was heated under reflux with water or acetic acid.

C. From 2-Methylol-2-(4-Piperidyl)-1,3-Dioxolane (**9**).

The ketal **9** (2) (0.1 g.) was dissolved in *ca.* 1 ml. of concentrated sulfuric acid by warming slightly on the steam bath; an orange solution formed. Water was added and the solution made basic with potassium carbonate. The mixture was extracted with methylene chloride and ether and the extracts concentrated. The residue was diluted with ether and treated with picric acid to yield 3-quinuclidinone picrate, 0.6 mg., m.p. 190-210°; when mixed with an authentic sample, the melting point was not depressed.

D. From 4-(Hydroxyacetyl)piperidine.

4-(Hydroxyacetyl)piperidine (2) was heated under reflux in various solvents (1% solutions): diglyme, diethylene glycol diethyl ether, water, acetophenone, xylene, tetrahydrofuran, dioxane and ethanol. Hydroxylic solvents (water, ethanol) apparently led to hydrolysis since low recovery of basic material resulted. Starting material was recovered from the low-boiling solvents. In higher boiling aprotic solvents, starting material was also recovered and polymeric material was formed. In refluxing diethylene glycol diethyl ether, product was isolated having strong carbonyl absorption at 1725 cm^{-1} from which 3-quinuclidinone picrate could be isolated, m.p. 200-210°.

1-Azabicyclo[3.2.1]octan-6-one Hydrobromide.

A solution of 1-benzyl-3-(hydroxyacetyl)piperidine (2) (0.35 g., 0.0015 mole) and 0.18 ml. of concentrated hydrobromic acid (0.0016 mole) in 50 ml. of acetophenone was heated under reflux for 1.5 hours. The solvent was removed by distillation under reduced pressure; the residue was diluted with ether and extracted four times with water. Concentration of the water extracts gave a residue containing crude 1-benzyl-1-azabicyclo[3.2.1]octan-6-one bromide (**5**) (ν 1750 cm^{-1}) which was dissolved in 50 ml. of absolute ethanol and hydrogenated with 0.5 g. of 10% palladium-charcoal catalyst (30 minutes, 22 psi, 24°). The catalyst was filtered and the filtrate concentrated to yield 0.16 g. (52%) of crude 1-azabicyclo[3.2.1]octan-6-one hydrobromide which was recrystallized from 2-propanol, m.p. 230-235°.

1-Azabicyclo[3.2.1]octan-6-one (**6**).

The hydrobromide salt of **6** was converted into the free base by treatment with saturated potassium carbonate solution followed by extraction with methylene chloride. Without isolation or purification the base was converted into its picrate derivative which was recrystallized from 2-propanol, m.p. 202-204°; ν (potassium bromide), 1760 cm^{-1} (C=O); when mixed with an authentic sample (11) the melting point was not depressed.

Anal. Calcd. for $C_{13}H_{14}N_4O_8$: C, 44.07; H, 3.98; N, 15.82. Found: C, 43.91; H, 3.87; N, 15.67.

2-(3-Quinuclidinyl)-1,3-dioxolane (**10**).

A. From 3-Quinuclidinone.

A mixture of 3-quinuclidinone (2.5 g., 0.02 mole), ethylene glycol (1.4 g., 0.022 mole), *p*-toluenesulfonic acid monohydrate (4.0 g., 0.021 mole) and 50 ml. of benzene was heated under reflux for 15.5 hours; 0.8 ml. of water was removed in a Dean-Stark trap during the heating. The mixture was cooled, treated with saturated potassium carbonate solution, filtered, and the precipitate washed with benzene. The benzene solution was separated, dried, and distilled to yield 2.7 g. (80%) of ketal **10**, b.p. 86-88° (3.3 mm.), n_D^{25} 1.4925, m.p. 17-19°. A redistilled sample had b.p. 89° (3.5 mm.). n_D^{25} 1.4939, m.p. 20-21°; carbonyl absorption bands were

absent in the infrared spectrum.

B. From 2-Methylol-2-(4-piperidyl)-1,3-dioxolane (**9**).

A 1.8-g. (0.01 mole) sample of ketal **9** and 1.0 g. of 5% rhodium on charcoal catalyst, contained in a 150 ml. stainless steel bomb pressurized with hydrogen (1900 psi, 25°), were heated with shaking at 240° for 5 hours. After cooling, the product was rinsed from the bomb with methylene chloride, the mixture filtered and the residue distilled to yield 0.07 g. (4%) of crude **10**, b.p. 80-90° (3.3 mm.) n_D^{25} 1.451, and 0.49 g. of undistillable residue. The infrared spectrum of the distilled product revealed essentially no NH, OH or C=O absorption bands and resembled closely that of authentic **10**. A picrate of the distillate was prepared, m.p. 155-158°, alone and when mixed with authentic **10** picrate.

Anal. Calcd. for $C_9H_{15}NO_2$: C, 63.88; H, 8.94; N, 8.28; mol. wt., 169.2. Found: C, 64.12; H, 9.15; N, 7.93; mol. wt., 174 (osmometry).

The picrate of **10** prepared from 3-quinuclidinone (method A) crystallized from water as large, lemon-yellow prisms, m.p. 156.5-158.5°.

Anal. Calcd. for $C_{15}H_{18}N_4O_9$: C, 45.23; H, 4.55; N, 14.07. Found: C, 45.68; H, 4.48; N, 14.28.

Hexahydro-1*H*, 3*H*-pyrido[1,2-*c*][1,3]oxazin-1-one Ethylene Ketal (**12**).

A solution of 2-hydroxymethyl-2-(2-piperidyl)-1,3-dioxolane (2) (0.935 g., 0.005 mole) and 35% formalin (0.7 ml., 0.008 mole) in 100 ml. of *N* hydrochloric acid after standing at 25° for 24 hours was heated on the steam bath (75-80° in liquid) in a glass-stoppered flask for 15 hours. The solution was concentrated under reduced pressure to a volume of 10 ml.; potassium carbonate was added to liberate the free base which was extracted with methylene chloride. The dried extracts were distilled to yield 0.85 g. (85%) of ketal **12**, b.p. 72-82° (13 mm.), n_D^{25} 1.4984; OH, NH, and C=O infrared absorption bands absent; nmr (deuteriochloroform) AB quartet, J_{AB} 7.5 Hz @ τ 5.72, 6.43 (2, C–4 CH_2); AB quartet, J_{AB} 11.5 Hz @ 6.27, 6.80 (2, C–2 CH_2); 6.11 (m, 4, OCH_2CH_2O), 7-9 (m, 9, piperidine ring); a similar nmr spectrum was observed in deuterioacetone; mass spectrum, m/e (% relative abundance): 28 (35), 42 (40), 55 (20), 68 (9), 69 (10), 83 (6), 86 (100), 87 (20), 96 (7), 97 (22), 112 (3), 126 (4), 138 (1), 169 (4), 198 (1), 199 (3) M*; metastable peaks at 197, 143.6, 122.2, 116.0, 49.1, 47.6, 37.0.

Anal. Calcd. for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03; mol. wt., 199.24. Found: C, 60.38; H, 8.74; N, 6.98; mol. wt., 199 (mass spectrometry).

The picrate derivative crystallized from 2-propanol as flat yellow prisms, m.p. 183-186°; nmr (acetone-d_6), AB quartet, J_{AB} 9.0 Hz @ τ 5.01, 5.42 (2, C–4 CH_2); AB quartet, J_{AB} 12.0 Hz @ 6.10, 6.37 (2, C–2 CH_2); 5.98 (m, 4, OCH_2CH_2O), 6.3-6.7 (m, 1, piperidine ring methine), 8.18 (m, 8, piperidine ring).

Anal. Calcd. for $C_{16}H_{20}N_4O_{10}$: C, 44.86; H, 4.71; N, 13.08. Found: C, 44.67; H, 4.73; N, 13.07.

A 0.1-g. sample of ketal **12** in 1 ml. of cencentrated hydrobromic acid at 25° for 70 hours was recovered unchanged (infrared spectrum).

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