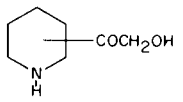
The Hydroxyacetylpiperidines and their *N*-Benzyl Derivatives. The 2-Hydroxymethyl-2-piperidyl- and 2-Hydroxymethyl-2-pyridyl-1,3-dioxolanes (1)

Arnold T. Nielsen and Ernest N. Platt

Organic Chemistry Branch, Chemistry Division
Michelson Laboratory, Naval Weapons Center

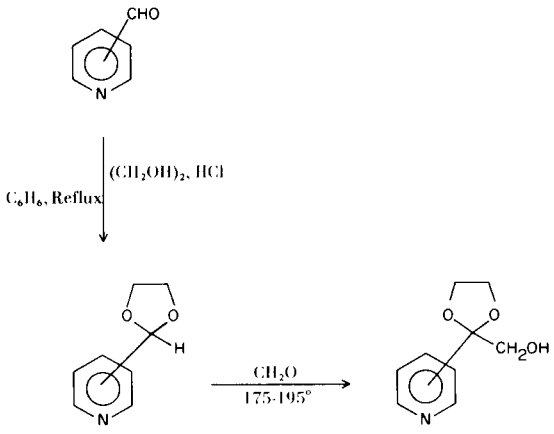
The hydroxyacetylpiperidines, their ethylene ketals, and the *N*-benzyl derivatives of these new piperidines have been synthesized. Methylolation of 2-(2- and 4-pyridyl)-1,3-dioxolanes by heating with paraformaldehyde at 185° led to 2-hydroxymethyl-2-(2- and 4-pyridyl)-1,3-dioxolanes (**7**,**8**, respectively). 2-Hydroxymethyl-2-(3-pyridyl)-1,3-dioxolane (**13**) was obtained by reaction of 2-bromomethyl-2-(3-pyridyl)-1,3-dioxolane with aqueous sodium hydroxide at 190°. Hydrogenation of these pyridine ketals with rhodium-charcoal catalyst produced the corresponding piperidine ketals (**16**,**17**,**18**). Acid hydrolysis of the piperidine ketals and their *N*-benzyl derivatives led to the hydroxyacetylpiperidines (**1**,**2**,**3**) and their *N*-benzyl derivatives (**25**,**26**,**27**). The *N*-benzylhydroxyacetylpiperidines undergo rapid hydrogenolysis with palladium-charcoal catalyst to produce the hydroxyacetylpiperidines. Further hydrogenation produces the piperidyl-1,2-ethanediols. The hydroxyacetylpiperidines are somewhat unstable, hygroscopic substances which polymerize with dehydration on standing; in solution they are relatively stable. Their *N*-benzyl, ketal, and hydrochloride salt derivatives, on the other hand, represent stable, synthetically useful intermediates from which the reactive trifunctional hydroxyacetylpiperidines may readily be prepared.

The hydroxyacetylpiperidines (**1**,**2**,**3**) represent very reactive, useful trifunctional intermediates. We report the first synthesis of these substituted piperidines and their ethylene ketals. New synthetic routes to the required hydroxyacetalpyridine ketal precursors were developed, since it was not possible to prepare these ketals directly from the known hydroxyacetylpyridines (2).



1 2-Piperidyl
2 3-Piperidyl
3 4-Piperidyl

The pyridinecarboxaldehydes, now readily available (3), were starting materials for synthesis of 2- and 4-hydroxyacetylpiperidines. The pyridinecarboxaldehyde ethylene acetals (**4**,**5**,**6**) were prepared in excellent yield employing hydrogen chloride catalyst in refluxing benzene (4).



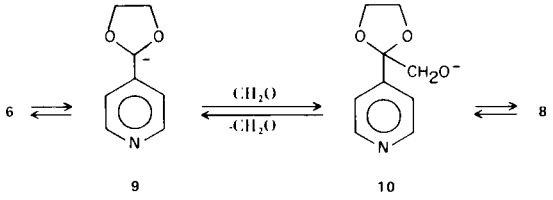
4 2-Pyridyl
5 3-Pyridyl
6 4-Pyridyl

7 2-Pyridyl
8 4-Pyridyl

Methylolation of pyridine-4-carboxaldehyde acetal (**6**) to form 2-hydroxymethyl-2-(4-pyridyl)-1,3-dioxolane (**8**) was achieved by heating with excess paraformaldehyde (3-5 mole-equivalents) for 2-3 hours at 175°. Conversions of 24-38% and yields of 92-98% were obtained in a batch process. With pyridine-2-carboxaldehyde acetal (**4**) at the

optimum temperature of 190-195°, under similar conditions, conversion to the methylol derivative **7** was 2-3%; yields were 86-90% based on recovered acetal. Yields of **7** and **8** were increased by employing a larger molar excess of formaldehyde. Prolonged reaction times and/or higher temperatures resulted in excessive tar formation and lower yields. Addition of basic catalysts (calcium oxide, sodium hydroxide) failed to improve yields. The methylolation reaction failed with pyridine-3-carboxaldehyde acetal (**5**).

The hydroxymethylpyridine ketals are remarkably stable in basic media. Ketal **8** was recovered unchanged after heating with aqueous sodium hydroxide at 185° for 1.6 hours. Both methylolation of anion **9** and demethylolation of anion **10** occur slowly.



Synthesis of 2-hydroxymethyl-2-(3-pyridyl)-1,3-dioxolane (**13**) was achieved by a different method (Scheme I). Bromination of 3-acetylpyridine in concentrated hydrobromic acid leads to 3-bromoacetylpyridine hydrobromide (**11**) in 91-96% yield (2a,c,5). The ethylene ketal of 3-bromoacetylpyridine (**12**) was prepared from **11** and ethylene glycol in refluxing benzene (24% yield) and hydrolyzed to ketal **13** by heating with aqueous sodium hydroxide at 190° (39% yield in 20 hours). Reaction of **12** with sodium acetate in acetonitrile at 185° led to acetate **15**, which in ethanolic sodium ethoxide also produced **13**. 3-Acetoxyacetylpyridine (**14**) (1c) with ethylene glycol and hydrogen chloride in refluxing benzene failed to form its ketal (**15**).

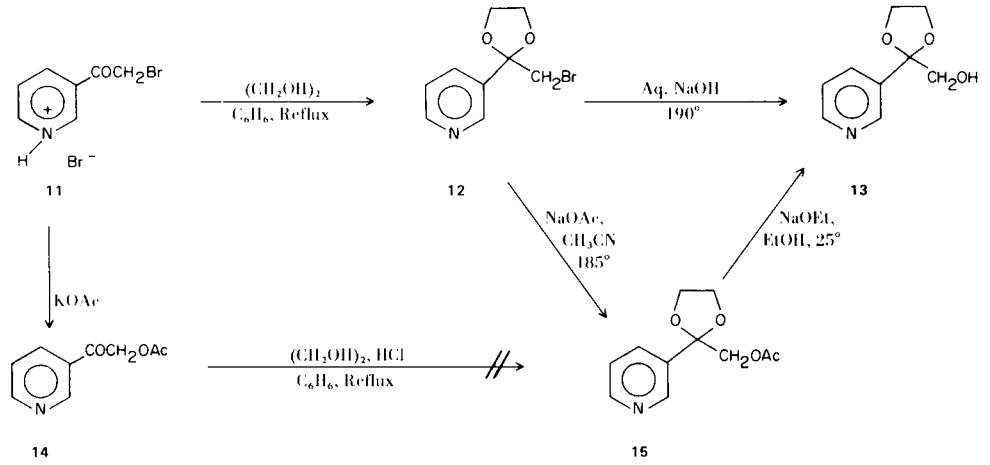
Hydrogenation of the pyridine ketals **7**, **13**, and **8** to the corresponding 2-hydroxymethyl-3-piperidyl-1,3-dioxolanes (**16**,**17**, and **18**, respectively) occurred readily with rhodium-charcoal catalyst in water solvent at 25°, 50 psi (70-90% yields); Scheme II.

Rates of hydrogenation of the three isomers differ considerably. Times required for absorption of one-half the theoretical amount of hydrogen under identical conditions (50 ml. of 0.2 molar aqueous solution, 1 g. of 5% rhodium-charcoal catalyst, 50 psi, 25°) were for 2-pyridyl **7** → **16**, 5 minutes; 3-pyridyl **13** → **17**, 150 minutes; and 4-pyridyl **8** → **18**, 700 minutes.

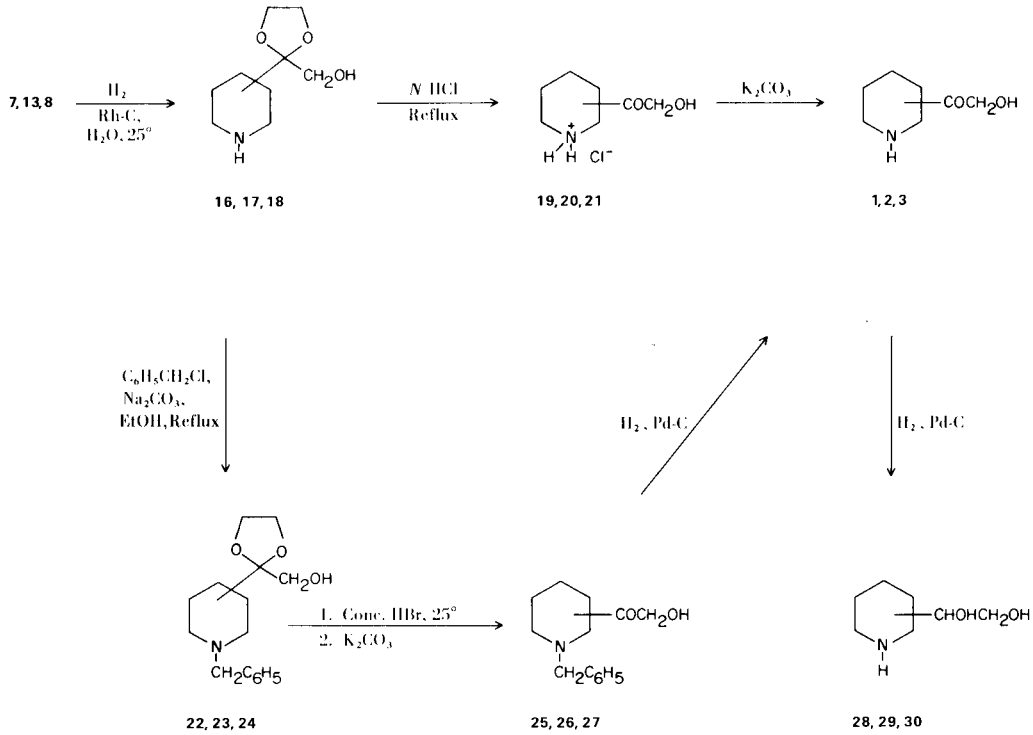
3- and 4-Hydroxyacetylpiperidine ketals (**17**,**18**) react with methylene chloride solvent to produce their hydrochloride salts (34 and 44% yields, respectively, after 3 days at 25°). On the other hand, 2-hydroxyacetylpiperidine ketal (**16**) under the same reaction conditions produced no hydrochloride salt after one month. Formation of salts of certain amines by reaction with halogenated solvents has been observed and studied by other workers (6).

Certain properties of 2-hydroxymethyl-2-(piperidyl)-1,3-dioxolane (**16**) differ noticeably from those of the 3- and 4-piperidyl isomers, **17** and **18**. The 2-isomer is a liquid having very high solubility in aprotic solvents such as benzene and ether, whereas **17** and **18** are crystalline solids of very low solubility in these solvents. Intramolecular hydrogen bonding in **16** is believed responsible for this difference in behavior. A strong OH· · · N intramolecular hydrogen bond absorption band is observed at 3297 cm^{-1} ($\triangle\nu$ 305 cm^{-1}) in dilute solutions of **16** in carbon tetrachloride; free OH and NH absorption bands appear at 3602 and 3325 cm^{-1}, respectively. The other isomers (**17** and **18**) in dilute carbon tetrachloride solu-

SCHEME I

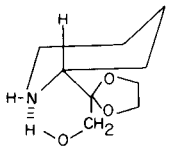


SCHEME II



1, 7, 16, 19, 22, 25, 28 (2-Piperidyl)
2, 13, 17, 20, 23, 26, 29 (3-Piperidyl)
3, 8, 18, 21, 24, 27, 30 (4-Piperidyl)

tions reveal only free OH and NH absorption bands at 3600 and 3350 cm^{-1}. Intramolecular OH· · · N bands in other amino alcohols appear at 3100-3550 cm^{-1} ($\triangle\nu$ 70-540 cm^{-1}) (7).



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The hydroxyacetylpiperidines (**1**,**2**,**3**) were synthesized by two routes (Scheme II). Their ketals (**16**,**17**,**18**) were hydrolyzed by heating under reflux with *N* hydrochloric acid to afford the hydrochloride salts of the ketols (**19**, **20**,**21**). The free ketol bases were liberated from the salts with potassium carbonate solution (90-100% over-all yield from the ketals). In a second route, hydrogenolysis of the *N*-benzyl derivatives (**25**,**26**,**27**) with palladium charcoal catalyst gave the hydroxyacetylpiperidines in 90-98% over-all yield from the *N*-benzyl ketals (**22**,**23**,**24**). These ketals were obtained in 92-98% yield by reaction of the piperidine ketals (**16**,**17**,**18**) with benzyl chloride and sodium carbonate in refluxing ethanol. Hydrolysis of these ketals to the *N*-benzylhydroxyacetylpiperidines occurred in concentrated hydrobromic acid at 25°.

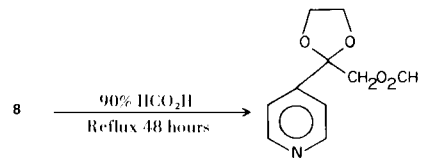
Hydrogenolysis of the *N*-benzylhydroxyacetylpiperidines (**25**,**26**,**27**) to ketols **1**, **2**, **3** occurs very readily. Further hydrogen uptake in the presence of palladium-charcoal catalyst is slow and leads to glycols. 2- and 4-Piperidyl-1,2-ethanediols (**28**,**30**) were obtained in quantitative yield by this reaction. These known viscous liquid glycols have been prepared from the appropriate vinylpyridines by oxidation, followed by reduction (8).

The *N*-benzylhydroxyacetylpiperidines (**25**,**26**,**27**) are reasonably stable substances and can be stored indefinitely in the refrigerator. The 4-piperidyl isomer (**27**) could be distilled at 0.2 mm. (m.p. 37-39°). However, the 2- and 3-isomers (**25**,**26**) could not be obtained crystalline, and attempted distillation resulted in their decomposition. The 2-isomer heated at 200-230° (0.6 mm.) dehydrated to produce an unidentified oil, believed to be a mixture containing α,β-unsaturated methyl ketones, $C_{13}H_{17}NO$.

The hydroxyacetylpiperidines are hygroscopic, water soluble substances. The 3-isomer was obtained crystalline (m.p. 108-110°), the 2- and 4- isomers as oils. The hydrochloride salts of the hydroxyacetylpiperidines (**19**,**20**,**21**) are stable substances, which are most conveniently prepared in solution *in situ* from the ketals. For reactions of hydroxyacetylpiperidines conducted in acidic media the stable ethylene ketals (**16**,**17**,**18**) serve as very convenient precursors. The free hydroxyacetylpiperidine bases are reasonably stable in dilute solution, and the solutions in water may be obtained simply by adding excess potassium carbonate to aqueous solutions of the amine hydrochloride salts. Solutions in methylene chloride or chloroform may be prepared.

The hydroxyacetylpiperidines polymerize with loss of water on standing at room temperature for a few days. Heating hastens the process. Attempted distillation under reduced pressure results in very rapid polymerization with dehydration. The polymeric products are brittle solids having carbonyl absorption at 1700 cm^{-1}. They are insoluble in all common solvents and decompose on heating, without melting, at 200-250°. Unstable 4-piperidylacetaldehyde exhibits behavior similar to that of hydroxyacetylpiperidines (9).

The interconversion of the known hydroxyacetylpyridines (2) and their ethylene ketals (**7**,**8**,**13**) could not be realized. Reaction of the ketols with ethylene glycol in refluxing benzene with hydrogen chloride catalyst failed to yield ketals; much polymeric material resulted. Also, attempted hydrolysis of the ketals (**7**,**8**,**13**) with various acid catalysts usually led to recovered reactant or polymeric material. The 4-isomer (**8**) is very resistant to hydrolysis. When refluxed with 90% formic acid for 48 hours there was obtained a 75% yield of formate ester **31** and 23% recovered ketal.



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EXPERIMENTAL (10)

2-(4-Pyridyl)-1,3-dioxolane (**6**).

Pyridine-4-carboxaldehyde, freshly distilled (245 g., 2.28 moles, b.p. 80-84° at 16 mm.) was dissolved in 800 ml. of benzene and the solution cooled in an ice bath. Hydrogen chloride (83.3 g., 2.28 moles) was passed into the cold solution during 20 minutes, precipitating the amine hydrochloride. Ethylene glycol (160 g., 2.5 moles) was added and the mixture heated under reflux, with stirring in a nitrogen atmosphere for 39 hours (oil bath temperature 130°). Water was removed in a Dean-Stark tube, 34 ml. being collected in 15 hours and 5 ml. additional thereafter. To the mixture containing tan crystals was added, during 20 minutes, a solution of 165 g. of 85% assay potassium hydroxide (2.5 moles) in 160 ml. of water, keeping the temperature between 20 and 30° with ice-bath cooling. The mixture was stirred vigorously for 3-4 hours. The benzene layer was separated and the aqueous part extracted three times with benzene. After drying the combined extracts and distilling the benzene, the residue was distilled through a short column to yield 295 g. (86%) of 2-(4-pyridyl)-1,3-dioxolane (**6**), b.p. 120-124° (11 mm.), m.p. 28-34°, and 13.8 g. of residue; lit. (11) b.p. 116-118° (9 mm.), m.p. 35-37°. The infrared spectrum of the product revealed no carbonyl absorption. In parallel runs yields of 86-90% were obtained. With *p*-toluenesulfonic acid catalyst substituted for hydrogen chloride, a bath temperature of 180°, and a reaction time of 4-15 hours, the yield of **6** was 53-56%.

2-(3-Pyridyl)-1,3-dioxolane (**5**).

This compound was prepared by the above procedure from 0.5 mole of pyridine-3-carboxyaldehyde using concentrated hydrochloric acid (one molar equivalent) rather than hydrogen chloride gas. A bath temperature of 113° and a reaction time of 21 hours gave a 93% yield of **5**, b.p. 112° (7 mm.), n^{25} 1.5235; lit. (4a) b.p. 97° (3 mm.), n_D^{20} 1.5257; lit. (12) b.p. 103-105° (3 mm.).

2-(2-Pyridyl)-1,3-dioxolane (**4**).

This compound was prepared from 0.7 mole of pyridine-2-carboxaldehyde by the procedure employed with the 3-isomer to give 57% yield of **4**, b.p. 103-104° (5 mm.), n_D^{25} 1.5224; a 2.5-mole run gave 40% yield; lit. (13) b.p. 122° (4 mm.), n_D^{25} 1.5225.

Anal. Calcd. for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.39; H, 6.09; N, 9.24.

2-Hydroxymethyl-2-(4-pyridyl)-1,3-dioxolane (**8**).

Procedure A.

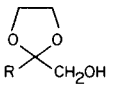
2-(4-Pyridyl)-1,3-dioxolane (**6**) (100 g., 0.67 mole) and paraformaldehyde (60 g., 2.0 moles) were introduced into a 300 ml. capacity stainless steel bomb and the temperature raised to 175° during 2.5 hours (agitation by rocking); the temperature was consecutively held at 175° for 2.5 hours, 175-150° for 0.5 hour and 150° for 1.5 hours. After cooling to room temperature the liquid product was poured into 100 ml. of 20% potassium hydroxide solution in a 1 l. beaker and heated on the steam bath for 5 hours. The solution was cooled, and sufficient potassium carbonate added to liberate the oily base. The mixture was extracted with methylene chloride and the extracts dried. Distillation through a short Claisen head gave (1) 51.7 g. of recovered acetal **6**, b.p. 80-90° (0.5 mm.), (2) 32.4 g. of crude **8**, b.p. 115-145° (0.3 mm.), and 7.0 g. of black tarry residue. Crystallization of fraction 2 from ether gave 30.1 g. (25% yield) of **8**, m.p. 71-72°. The alkali treatment destroys excess paraformaldehyde and facilitates the vacuum distillation.

Procedure B.

In a parallel run the liquid reaction product was concentrated under reduced pressure on the steam bath to yield: (1) 63.1 g. of recovered **6**, b.p. 95-100° (1.5-4 mm.); (2) 40.7 g. b.p. 125-140° (< 0.3 mm.), containing **6** and **8**; and (3) 9.6 g. of residue. Fraction 2 was crystallized from ether (50 ml.) to yield 29.4 g. (24.5% conversion, 96% yield) of 2-methylol-2-(4-pyridyl)-1,3-dioxolane (**8**), m.p. 73-75°. Parallel runs gave 24-38% conversion, 92-98% yields. Recrystallization from ether gave prisms, m.p. 75-76° (Table I); ν cm^{-1} 3250 (OH), carbonyl absorption absent; nmr

TABLE I

Pyridyl-, Piperidyl-, and *N*-Benzylpiperidyl-2-hydroxymethyl-1,3-dioxolanes



Compound	R	M.p. or b.p., °C	Molecular formula	Elemental analyses found %C	%H	%N	Mol. wt.
7	2-Pyridyl	120-121	$C_9H_{11}NO_3$(a)	59.65	6.07	7.52	
13	3-Pyridyl	71-72	$C_9H_{11}NO_3$ (a)	59.49	6.17	7.62	
8	4-Pyridyl	75-76	$C_9H_{11}NO_3$ (a)	59.65	6.18	7.78	
16	2-Piperidyl	88-90 (0.1 mm.)	$C_9H_{17}NO_3$ (b)	57.54	9.32	7.25	186 (c)
17	3-Piperidyl	83-84	$C_9H_{17}NO_3$ (b)	57.54	9.00	7.45	190 (c)
18	4-Piperidyl	113-114	$C_9H_{17}NO_3$ (b)	57.91	8.98	7.64	197 (c,d)
22	*N*-Benzyl-2-piperidyl	144-146 (0.1 mm.) (e,f)	$C_{16}H_{23}NO_3$ (g)	69.49	8.49	5.04	
23	*N*-Benzyl-3-piperidyl	(h)	$C_{16}H_{23}NO_3$ (g)	69.13	8.60	4.74	
24	*N*-Benzyl-4-piperidyl	50-52 (i)	$C_{16}H_{23}NO_3$ (g)	69.61	8.51	5.37	

(a) Calcd. for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. (b) Calcd. for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48; nol. wt., 187.23. (c) Molecular weight determined by vapor osmometry. (d) Neutral equivalent found, 194; calcd. 187.23. (e) n_D^{25} 1.5460. (f) Hydrobromide salt, m.p. 196-199° (*i*-PrOH); *Anal.* Calcd. for $C_{16}H_{24}NO_3Br$: C, 53.63; H, 6.75; N, 3.91. Found: C, 53.88; H, 7.10; N, 4.01. (g) Calcd. for $C_{16}H_{23}NO_3$: C, 69.28; H, 8.36; N, 5.05. (h) n_D^{25} 1.5483; undistilled oil. (i) B.p. 162-166° (0.1 mm.) with some decomposition.

(deuteriochloroform); τ 1.50 (d, J = 6 Hz, 2, 2,6-pyridyl protons); 2.57 (d, J = 6 Hz, 2, 3,5-pyridyl protons); 5.26 (s, 1, CH_2OH); 6.25 (s, 2, CH_2OH); A_2B_2 multiplet = τ_A 5.89, τ_B 6.12 (4, OCH_2CH_2O).

The filtrate remaining after crystallization of product **8** from fraction 2 was shown to contain principally recovered reactant (**6**). Distillation of the combined filttated from several such runs provided *ca.* 88% recovered **6**, 7.5% additional methylol compound **8** and 4.5% undistillable residue. To simplify calculation of yields, without introducing significant errors, the uncrystallizable portion of fraction 2 is assumed to be reactant.

A *picrate* derivative of **8** was prepared in water to yield chunky crystals, m.p. 162-165°. Recrystallization from 95% ethanol gave long prisms, m.p. 141-142°.

Anal. Calcd. for $C_{15}H_{14}N_4O_{10}$: C, 43.91; H, 3.44; N, 13.66. Found: C, 44.15; H, 3.14; N, 14.26.

This conversion to **8** was increased by use of higher molar ratios of formaldehyde to **6**. At 185° (2.5 hours) in a 300 ml. stainless steel bomb with the quantities: moles of paraformaldehyde: moles of ketal **6** gave % conversions to **8** indicated in parentheses: 1.0:1.0 (12.5%); 2.0:1.0 (20%); 2.0:0.67 (29%); 2.0:0.50 (38%); yields based on recovered **6** were 89-95% in these runs. Formaldehyde in excess of 5 mole-equivalents resulted in a product difficult to purify; crystals of **8** which separated from the ether solvent were oily.

A 0.45-g. sample of 2-hydroxymethyl-2-(4-pyridyl)-1,3-dioxolane (**8**) in 50 ml. of water was treated with 10 ml. of 10% aqueous sodium hydroxide solution and heated to 185° in a stainless steel bomb during 2.4 hours and at 185° for 1.6 hours. Isolation of the product in the usual manner gave 0.45 g. (100%) of recovered **8**, m.p. 72-74°.

2-Formyloxymethyl-2-(4-pyridyl)-1,3-dioxolane **31**.

A solution of 2-hydroxymethyl-2-(4-pyridyl)-1,3-dioxolane **8** (0.9 g., 0.005 mole) in 99% formic acid (15 ml.) and 1.5 ml. of water was heated under reflux for 48 hours. The solution was concentrated to remove solvents, treated with saturated potassium carbonate solution, and extracted with methylene chloride. The dried extracts were concentrated to dryness and the residue extracted with hot hexane to yield, on chilling, 2-formyloxymethyl-2-(4-pyridyl)-1,3-dioxolane (**31**; 0.52 g., m.p. 27-29°, and 0.27 g., m.p. 34-35°; total 0.79 g., 76% yield) and 0.21 g. (23%) of recovered **8**, m.p. 59-60°. Recrystallization gave pure **31**; prisms, m.p. 34.5-35°; ν neat 1720 cm^{-1} (C=O, formate ester).

Anal. Calcd. for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70; mol. wt., 209.2. Found: C, 57.55; H, 5.30; N, 6.70; mol. wt., 227 (osmometry).

2-Hydroxymethyl-2-(2-pyridyl)-1,3-dioxolane (**7**).

The method employed in the preparation of the 4-pyridyl isomer (Procedure A) was used with 96.5 g. (0.65 mole) of 2-(2-pyridyl)-1,3-dioxolane (**4**) and 96.5 g. (3.2 moles) of paraformaldehyde. The temperature was raised to 195° during 5 hours and maintained at 195° for 2.5 hours. After workup the product was distilled at 0.4 mm. to yield 78.5 g. (81.5%) of recovered acetal **4**, b.p. 90-95°; 7.2 g., b.p. 104-130°, and 9.1 g. of residue. Trituration of the second fraction with ether gave 3.6 g. of crude **7**, m.p. 95-110°. Recrystallization from benzene gave 2.2 g. of **7**, (2% conversion) m.p. 119-121°. Further recrystallization from ether

raised the melting point to 120-121°; Table I. The yield, based on recovered acetal, is 87%. In parallel runs conversions of 1-2% and yields of 86-90% were realized.

4-Chloroacetylpyridine Hydrochloride.

Dry chlorine was slowly passed into a solution of 4-acetylpyridine (12.1 g., 0.1 mole) in 150 ml. of chloroform during 3 hours keeping the temperature at 25° for 16 hours. The mixture was concentrated to a small volume and filtered to yield 17.1 g. of crude 4-chloroacetylpyridine hydrochloride [65-70% assay, containing 30-35% of 4-acetylpyridine hydrochloride (ν 1700 cm^{-1}; potassium bromide) by infrared analysis]. Recrystallization from acetonitrile gave white crystals of 4-chloroacetylpyridine hydrochloride, m.p. 250-255°, dec. (capillary); ν (potassium bromide) 1725 cm^{-1}

Anal. Calcd. for $C_7H_7Cl_2NO$: C, 43.77; H, 3.67; Cl, 36.93; N, 7.29. Found: C, 43.46; H, 4.01; Cl, 37.08; N, 7.30.

Reaction of 4-chloroacetylpyridine hydrochloride with sodium hydroxide or sodium acetate led to dark oils or tars. Reaction with ethylene glycol in refluxing benzene (20 hours, oil bath temperature 125°) gave much tar and some dark oil.

3-Bromoacetylpyridine Hydrobromide (**11**).

Freshly distilled 3-acetylpyridine (121.1 g., 1.0 mole) was added all at once to 120 ml. of concentrated hydrobromic acid (temperature rise to 65°). Bromine (160 g., 1.0 mole) was added dropwise with stirring during 1 hour keeping the temperature of the solution at 80-95° by heating on the steam bath. Shortly after addition of the last portion of bromine, the hydrobromide salt crystallized rapidly. After cooling to 0° the product was filtered through a sintered glass funnel and washed with cold water to yield 232.6 g. (83%) of **11** as white crystals, m.p. 195-196° (capillary); lit. m.p. 198° (5a), 191-192.5° (2c). The filtrate was treated with 10 ml. of bromine and allowed to stand for several days to deposit 32.3 g. of additional product, m.p. 188-197°; total yield, 264.9 g., 93%. Parallel runs gave 91-96% total yields of similar product.

Anal. Calcd. for $C_7H_7Br_2NO$: C, 29.93; H, 2.51; Br, 56.88; N, 4.98. Found: C, 29.90; H, 2.49; Br, 56.62; N, 5.04.

2-Bromomethyl-2-(3-pyridyl)-1,3-dioxolane (**12**).

3-Bromoacetylpyridine hydrobromide (**11**, 73 g., 0.26 mole), ethylene glycol (16 g., 0.26 mole) and 300 ml. of benzene were heated under reflux for 28 hours (oil bath temperature 95°) with vigorous stirring and a stream of nitrogen passing through the system; 4.2 ml. of water (90%) was collected in the Dean-Stark trap. The solution was cooled to 10° and a solution of 40 g. of potassium hydroxide in 100 ml. of water was added with stirring. After continued stirring for 18 hours the benzene layer was separated and the black aqueous layer extracted four times with 150-ml. portions of benzene. The combined extracts were dried and concentrated and the residue distilled at 0.5 mm. through a short column to yield 2.5 g., b.p. 60-68°; 15.3 g. of crude ketal **12**, b.p. 110-124°; and 4 g. of residue. Crystallization of fraction 2 from cyclohexane gave 13.1 g. (23%) of **12**, m.p. 35-40°; recrystallization gave prisms, m.p. 37.5-38.5°. Parallel runs gave yields of 15-24%.

Anal. Calcd. for $C_9H_{10}BrNO_2$: C, 44.25; H, 4.13; N, 5.74; Br, 32.74. Found: C, 44.54; H, 4.28; N, 5.67; Br, 32.63.

2-Hydroxymethyl-(3-pyridyl)-1,3-dioxolane (**13**)

Procedure A. From Bromoketal **12**.

A mixture of 12.2 g. (0.05 mole) of 2-bromomethyl-(3-pyridyl)-1,3-dioxolane (**12**), 20 g. of sodium hydroxide, 1.0 g. of potassium iodide, and 1.0 g. of sodium acetate in 150 ml. of water was heated in a 300-ml. capacity stainless steel bomb at 190°, with rocking, for 20 hours. The resulting clear yellow liquid was concentrated in vacuum on the steam bath, treated with potassium carbonate, and extracted with methylene chloride. Concentration of the dried extracts gave 5.9 g. of oil which was extracted with 270 ml. of boiling ether. Chilling and concentration of the extracts gave 3.54 g. (39%) of **13**, m.p. 69-71°. Recrystallization from ether gave chunky prisms, m.p. 71-72°; ν (mull) 3400 cm^{-1} (OH); Table I. A parallel run gave 39.5% yield.

Procedure B. From 2-Acetoxymethyl-(3-pyridyl)-1,3-dioxolane (**15**).

2-Bromomethyl-(3-pyridyl)-1,3-dioxolane (**12**, 5.45 g., 0.022 mole) and sodium acetate (2.0 g.) in 40 ml. of acetonitrile were heated in a stainless steel bomb at 180° for 12 hours. The mixture was concentrated, treated with saturated potassium carbonate and extracted with methylene chloride. The dried extracts were distilled at 0.4 mm. to yield 2.0 g. of recovered ketal **12**, b.p. 110-112°, and 0.81 g. of crude 2-acetoxymethyl-(3-pyridyl)-1,3-dioxolane (**15**), b.p. 120-140°; ν (neat) 1750 cm^{-1} (C=O, acetate). Without further purification the crude acetate (0.81 g.) was dissolved in 75 ml. absolute methanol containing 0.1 g. of sodium ethoxide and allowed to stand at 25° for 19 hours. The solution was concentrated, treated with saturated potassium carbonate solution and extracted with methylene chloride. The dried extracts were concentrated and the residue crystallized from ether to yield 0.22 g. of hydroxymethyl ketal **13**, m.p. 70-71°. Evaporation of the filtrate gave 0.3 g. of oil (infrared spectrum identical with that of bromoketal **12**).

2-Hydroxymethyl-2-(4-piperidyl)-1,3-dioxolane (**18**).

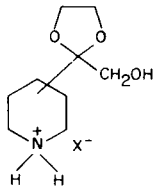
2-Hydroxymethyl-2-(4-pyridyl)-1,3-dioxolane (**8**, 50 g., 0.276 mole) in 150 ml. of water was hydrogenated in a Parr apparatus with 25 g. of 5% rhodium on charcoal catalyst (30-50 psi, 45°, 72 hours). The catalyst was filtered and extracted twice with 50 ml. portions of hot water by digestion on the steam bath. The combined solutions were distilled and concentrated under vacuum on the steam bath to remove volatile materials leaving 44.6 g. (86.5%) crystalline **18**, m.p. 108-110°. (In other parallel runs yields of 86-100% were obtained.) The crude product is quite pure; it may be readily recrystallized from 400 ml. of boiling acetone in which it very slowly dissolves; recovery, 34.6 g., m.p. 110-112°. Several recrystallizations from acetone provided a sample for analysis (Table I); prisms, m.p. 113-114°; ν cm^{-1} (potassium bromide) 3100 (NH), 3250 (OH); nmr (deuterium oxide): τ 6.0 (s, 4, OCH_2CH_2O), 6.46 (s, 2, CH_2OH), 6.7-9.0 (m, 9, piperidine ring). A picrate derivative was prepared (Table II).

2-Hydroxymethyl-2-(3-piperidyl)-1,3-dioxolane (**17**).

The procedure employed with the 4- isomer with 2-hydroxymethyl-2-(3-pyridyl)-1,3-dioxolane (**13**, 3.53 g., 0.0195 mole) and 1.5 g. 5% rhodium-charcoal catalyst in 50 ml. of water (50 psi, 26°, 22 hours) gave 3.3 g. of viscous oil which was heated under reflux with 3 l. of ether until dissolved (0.1 g. of insoluble residue remained). Concentration of the extracts and chilling gave 2.76 g. of **17** (76% yield), m.p. 81-83°. Recrystallization from ether gave a sample, m.p. 83-84° (Tables I, II); nmr (deuteriochloroform). τ 6.02 (s, 4, OCH_2CH_2O); 6.52 (s, 2, CH_2OH); 6.61 (s, 1, CH_2OH); 9.0 (m, 10, piperidine ring).

TABLE II

Salts of 2-Hydroxymethyl-2-piperidyl-1,3-diocolanes



Piperidyl substn.	Anion, X^-	M.p., °C;	Recrystn. solvent	Molecular formula	Elemental analyses found %C	%H	%N	%Cl
2-	Chloride	233-235°	*i*-PrOH	$C_9H_{18}ClNO_3$ (a)	48.17	8.17	6.30	15.74
3-	Chloride	180-181°	Et_2O	$C_9H_{18}ClNO_3$ (a)	48.02	8.11	6.05	16.04
4-	Chloride	200-201°	*i*-PrOH	$C_9H_{18}ClNO_3$ (a)	48.41	8.13	6.27	16.17
2-	Picrate	141-141.5°	*i*-PrOH	$C_{15}H_{20}N_4O_{10}$ (b)	43.67	4.60	13.42	
3-	Picrate	204-206°	EtOH	$C_{15}H_{20}N_4O_{10}$ (b)	43.25	4.84	13.16	
4-	Picrate	150.5-152°	H_2O	$C_{15}H_{20}N_4O_{10}$ (b)	42.84	4.51	13.38	

(a) Calcd. for $C_9H_{18}ClNO_3$: C, 48.32; H, 8.11; N, 6.26; Cl, 15.85. (b) Calcd. for $C_{15}H_{20}N_4O_{10}$: C, 43.27; H, 4.84; N, 13.46.

2-Hydroxymethyl-2-(2-piperidyl)-1,3-dioxolane (**16**).

The procedure employed with the 3- and 4- isomers with 1.81 g. (0.01 mole) of 2-hydroxymethyl-2-(2-pyridyl)-1,3-dioxolane (**7**) (50 psi, 25°, 50 minutes) gave 1.7 g. of viscous colorless oil which was distilled to yield 1.3 g. (70%) of **16**, b.p. 88-91° (0.1 mm.), n_D^{25} 1.4980 (Tables I, II); nmr (deuteriochloroform), τ 6.01 (s, 4, OCH_2CH_2O), 6.32 (s, 1, CH_2OH), 6.40 (s, 2, CH_2OH), 6.5-9.0 (m, 10, piperidine ring). A parallel run with 3.62 g. of **7** gave 3.5 g. of **16**.

Reaction of 2-Hydroxymethyl-2-(piperidyl)-1,3-dioxolanes with Methylene Chloride. Formation of Hydrochloride Salts.

2-Hydroxymethyl-2-(4-piperidyl)-1,3-dioxolane (**18**, 0.20 g. recrystallized, undistilled) was dissolved in 20 ml. of methylene chloride and allowed to stand at 25° for 120 hours. Crystals of the hydrochloride salt of **18** (0.10 g., 42%) deposited, m.p. 200-201°; Table II. A distilled sample of **18** in a parallel experiment gave 44% yield of the hydrochloride salt, m.p. 200-201°, after 72 hours.

2-Hydroxymethyl-2-(3-piperidyl)-1,3-dioxolane (**17**, 0.050 g. recrystallized, undistilled) in 5 ml. of methylene chloride after standing 72 hours at 25° deposited 0.020 g. (34%) of the hydrochloride salt, m.p. 179-181°; recrystallization from ether gave prisms, m.p. 180-181°; Table II. The free base (**17**) was recovered after treatment of the hydrochloride salt with aqueous potassium carbonate and extraction with methylene chloride, m.p. 80-82°; melting point was not depressed when mixed with an authentic sample, m.p. 83-84°.

2-Hydroxymethyl-2-(2-piperidyl)-1,3-dioxolane (**16**, distilled or undistilled) in methylene chloride solution gave no precipitate after one month at 25°. Evaporation of the solvent and dilution of the residue with ether produced only a few crystals. The hydrochloride salt of **16** was readily prepared by reaction of the free base with hydrogen chloride in 2-propanol solvent and recrystallization from this solvent, m.p. 233-235° (Table II); nmr (deuterium oxide), τ 5.85 (s, 4, OCH_2CH_2O), 6.39 (s, 2, CH_2OH), 6.3-8.6 (m, 9, piperidine ring).

2-Hydroxymethyl-2-[4-(1-benzylpiperidyl)]-1,3-dioxolane (**24**).

Benzyl chloride (23.4 g., 0.184 mole) and 2-hydroxymethyl-2-(4-piperidyl)-1,3-dioxolane (**18**, 35.4 g., 0.184 mole) were dissolved in 250 ml. of absolute ethanol and 10 g. (0.092 mole) of powdered, anhydrous sodium carbonate added. The mixture was heated under reflux for 4 hours, and then concentrated under reduced pressure on the steam bath to remove volatiles. To the residue was added saturated potassium carbonate solution and ether and the mixture stirred to dissolve the residue. The ether layer was separated and dried with magnesium sulfate. Removal of the ether gave 46.2 g. (91.5%) of **24** as a viscous oil having an infrared spectrum identical with that of the distilled product (67% recovery), b.p. 162-166°; (0.1 mm.); Table I; the distillate solidified after long standing, m.p. 50-52°; ν 3450 cm^{-1} (OH) (supercooled liquid). Some decomposition accompanied the distillation.

2-Hydroxymethyl-2-[3-(1-benzylpiperidyl)]-1,3-dioxolane (**23**).

The procedure employed with the 4-isomer was used with 2-hydroxymethyl-2-(3-piperidyl)-1,3-dioxolane (**17**) except for a reflux time of 6 hours. The product was extracted with methylene chloride, and subsequently pumped at 0.1 mm., 25°, to remove volatiles; viscous oil, n_D^{25} 1.5483 (92-96% yield); Table I. The compound was not distilled.

2-Hydroxymethyl-2-[2-(1-benzylpiperidyl)]-1,3-dioxolane (**22**).

The procedure employed with the 3- and 4- isomers was used with 2-hydroxymethyl-2-(2-piperidyl)-1,3-dioxolane (**16**) except for a reflux time of 24 hours; reflux periods of 4-6 hours gave incomplete benzylation. The product, isolated by the procedure employed with the 3-isomer, was obtained as a viscous oil; n_D^{25} 1.5460; (97-98% yield); Table I; b.p. 144-146° (0.1 mm.) with some decomposition.

TABLE III

Hydroxyacetylpiperidine Derivatives

$RCOCH_2OH$

Compound	R	M.p., °C	Molecular formula	Elemental analyses found %c	%H	%N	%Cl,Br
20	3-Piperidyl.HCl	143-146°	$C_7H_{14}ClNO_2$ (a)	47.08	7.95	7.71	20.03
21	4-Piperidyl.HCl	166-168°	$C_7H_{14}ClNO_2$ (a)	46.99	7.97	7.67	19.90
25	*N*-Benzyl-2-piperidyl	oil (b)	$C_{14}H_{19}NO_2$ (c)	70.81	8.50	5.67	
26	*N*-Benzyl-3-piperidyl	oil (d)	$C_{14}H_{19}NO_2$ (c)	7.192	8.24	5.90	
27	*N*-Benzyl-4-piperidyl	37-39° (e)	$C_{14}H_{19}NO_2$ (c)	71.89	8.31	6.05	
	N-Benzyl-4-piperidyl.HCl	206-213°	$C_{14}H_{20}ClNO_2$ (f)	62.06	7.34	4.99	12.97
	N-Benzyl-4-piperidyl.HBr	224-227°	$C_{14}H_{20}BrNO_2$ (g)	53.29	6.41	4.47	25.47

(a) Calcd. for $C_7H_{14}ClNO_2$: C, 46.80; H, 7.86; N, 7.80; Cl, 19.74. (b) n_D^{25} 1.5430 for undistilled sample; decomposes on attempted distillation. (c) Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00; mol. wt., 233.3. (d) n_D^{25} 1.5478 for undistilled sample; decomposes on attempted distillation. (e) B.p. 150-154° (0.2 mm.), n_D^{25} 1.5478; found mol. wt. 235 (osmometry). (f) Calcd. for $C_{14}H_{20}ClNO_2$: C, 62.33; H, 7.47; N, 5.19; Cl, 13.15. (g) Calcd. for $C_{14}H_{20}BrNO_2$: C, 53.51; H, 6.42; N, 4.46; Br, 25.43.

1-Benzyl-4-(hydroxyacetyl)piperidine Hydrobromide.

A 27.7 g. (0.1 mole) sample of the undistilled detal **24** was dissolved in concentrated hydrobromic acid (100 ml.) and allowed to stand overnight at 25°. The crystals which deposited were filtered and washed with ice-water (22.1 g.); the filtrate chilled at 0° to deposit an additional 6.1 g.; total yield 28.2 g. (90%), m.p. 220-225°. Recrystallization from water gave large chunky crystals, m.p. 224-227°; Table III; ν cm^{-1} (potassium bromide), 1725 (C=O), 2500-3300 (OH, broad).

1-Benzyl-4-(hydroxyacetyl)piperidine (**27**).

1-Benzyl-4-(hydroxyacetyl)piperidine hydrobromide (15.7 g., 0.05 mole) was dissolved in 100 ml. of warm water and the solution made basic with potassium carbonate. The mixture was extracted with ether three times and the combined dried extracts concentrated to yield 11.4 g. (98%) of **27** having an infrared spectrum identical to a distilled sample, b.p. 150-154° (0.2 mm.); 90% recovery, n_D^{25} 1.5478; the distillate solidified on standing, m.p. 37-39°; Table III; ν cm^{-1} (neat), 3450 (OH), 1700 (C=O). The hydrobromide salt was regenerated from an ether solution of **27**, m.p. 220-224°. Heating **27** in aqueous ethanolic silver nitrate solution rapidly produced a silver mirror.

The hydrochloride salt of **27** was prepared by passing hydrogen chloride into an ether solution of the free base; recrystallization from aqueous ethanol gave chunky prisms, m.p. 206-213°; Table III. Its infrared spectrum, like that of the hydrobromide salt, showed no sharp hydroxyl absorption bands. The hydrochloride salt is much more soluble in water than the corresponding hydrobromide. It does not precipitate from solution when the ketal **24** is treated with concentrated hydrochloric acid.

A phenylosazone derivative was prepared by heating under reflux for 9 hours, a mixture of 1.07 g. of ketol **27**, 2.2 g. of phenylhydrazine hydrochloride and 3.3 g. of sodium acetate in 30 ml. of 50% aqueous ethanol; cooling gave 1.84 g. of yellow needles, m.p. 140-175°. Two recrystallizations from 95% ethanol gave small prisms, m.p. 162-165°, which after standing overnight melted at 154-156°. Further recrystallization from 95% ethanol gave small yellow prisms, m.p. 154-156°.

Anal. Calcd. for $C_{26}H_{29}N_5 \cdot 2.5H_2O$: C, 68.39; H, 7.51; N, 15.34. Found: C, 68.86; H, 6.95; N, 15.56.

1-Benzyl-3-(hydroxyacetyl)piperidine (**26**).

A solution of ketal **23** (1.63 g.) in 6 ml. of concentrated hydrobromic acid was allowed to stand at 25° for 24 hours. The clear solution was concentrated to a small volume in vacuum on the steam bath (no crystals separated) and the residue treated with excess saturated potassium carbonate solution. Extraction with methylene chloride, followed by drying and concentration, gave 1.37 g. (100%) of ketol **26** as a viscous oil, n_D^{25} 1.5478; Table III; ν cm^{-1} (neat), 3350 (OH), 1700 (C=O). An attempt to distil the material (bath temperature to 220°, 0.2 mm.) led to its complete decomposition with formation of a black solid residue.

1-Benxyl-2-(hydroxyacetyl)piperidine (**25**).

The procedure employed with the 3-isomer was used with ketal **22** (3 days at 25°) to yield the ketol **25** as a viscous oil, 90-98% yield, n^{25} 1.5430; Table III. Difficulty was experienced securing satisfactory elemental analyses.

Distillation of the material (bath temperature to 230°, 0.6 mm.) led to extensive decomposition with formation of a black solid residue and an oil (16% yield), b.p. 124-125° (0.5 mm.), n_D^{25} 1.5425, ν cm^{-1} (neat), 1710 (C=O), 1680 (C=C). The unidentified oil appears to be a dehydration product.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89; mol. wt., 203.3. Found: C, 76.40; H, 8.45; N, 6.80; mol. wt.,

201 (osmometry).

Its infrared and nmr spectra suggest a mixture of α,β-unsaturated methyl ketones; nmr principal peaks (deuteriochloroform), at τ 2.71 (m, C_6H_5), 3.95 (s, =CH), 6.07 (s, CH_2), 7.68 (s, CH_3), 7.8-8.8 (m, aliphatic protons).

4-(Hydroxyacetyl)piperidine Hydrochloride.

A 7.6 g. sample of ketal **18** in 100 ml. of *N* hydrochloric acid was heated under reflux for 2 hours. The solution was concentrated to dryness under reduced pressure while heating on the steam bath. Addition of 2-propanol and ether to the residue gave 7.8 g. of crude 4-(hydroxyacetyl)piperidine hydrochloride, m.p. 150-160°; recrystallization from absolute ethanol gave prisms, m.p. 166-168°; ν cm^{-1} (mull), 3350 ((H), 1700 (C=O); Table III.

3-(Hydroxyacetyl)piperidine Hydrochloride.

The above compound was prepared by the same procedure from ketal **17**; reflux time of 8 hours; Table III.

2-(Hydroxyacetyl)piperidine Hydrochloride.

This compound, prepared from ketal **16** (19 hours heating on steam bath), was obtained as an oil which could not be crystallized.

4-(Hydroxyacetyl) piperidine (**3**).

A. From 2-Hydroxymethyl-2-(4-piperidyl)-1,3-dioxolane (**18**).

A 1.0-g. sample of ketal **18** in 100 ml. of *N* hydrochloric acid was heated under reflux for 64 hours. The solution was concentrated to a small volume, made strongly alkaline with potassium carbonate and extracted with methylene chloride. The dried extracts were concentrated to yield 0.62 g. (100%) of **3** as a viscous oil; ν cm^{-1} (neat), 3300 (OH), 1700 (C=O). 4-(Hydroxyacetyl)-piperidine may also be liberated from its pure hydrochloride salt by the same procedure.

B. From 1-Benzyl-4-(hydroxyacetyl)piperidine (**27**).

A 2.33-g. (0.01 mole) sample of ketol **27** dissolved in 50 ml. of absolute ethanol was hydrogenated with 0.5 g. of 10% palladium-charcoal catalyst by shaking in a Parr apparatus for 1 hour at 50 psi, 25°. One mole-equivalent of hydrogen was absorbed in 30 minutes after which time hydrogen uptake proceeded very slowly. The mixture was filtered and the filtrate concentrated to yield 1.5 g. (100%) of 4-hydroxyacetylpiperidine (**3**). The viscous, oily product which failed to crystallize has an infrared spectrum identical to that of the sample obtained by method A. Satisfactory elemental analyses could not be obtained.

Attempts to purify the free base by distillation (bath temperature 155°, pressure 0.4 mm.) resulted in its rapid conversion into a solid, polymeric material, completely insoluble in water and organic solvents (including hot dimethyl sulfoxide, dimethylformamide, acetone and methylene chloride). The material does not melt, but darkens and decomposes on heating at 200-250°; ν cm^{-1} (mull), 3300, (weak, NH or OH), 1700 (strong, C=O).

Anal. Calcd. for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19. Calcd. for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 63.75; H, 9.02; N, 10.70.

A 2,4-dinitrophenylhydrazone hydrochloride of **3** was prepared, recrystallized from ethanol, m.p. 235-236° (decomposition).

Anal. Calcd. for $C_{13}H_{18}ClN_5O_5 \cdot 0.5\ H_2O$: C, 42.34; H, 5.19; Cl, 9.61; N, 18.99. Found: C, 42.43; H, 5.49; Cl, 9.42; N, 18.40.

3-(Hydroxyacetyl)piperidine (**2**).

The above compound was prepared from its ketal (**17**) by method A and from its *N*-benzyl derivative (**26**) by method B used for preparation of 4-(hydroxyacetyl)piperidine (90-100% yeild); prisms from ether, m.p. 108-110°. On standing at 25° for a few days the sample became gummy, non-crystalline.

Anal. Calcd. for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; mol. wt., 143. Found: C, 58.89; H, 8.99; mol. wt., 151 (osmometry, DMF).

2-(Hydroxyacetyl)piperidine (**1**).

The above compound was prepared from its ketal (**16**) by method A and from its *N*-benzyl derivative (**25**) by method B used for preparation of 4-(hydroxyacetyl)piperidine (90-100% yield). The material, like 4-isomer **3**, was an oil which changed to a gummy solid on standing a few days; satisfactory elemental analyses could not be obtained.

1-(4-Piperidyl)-1,2-ethanediol (**30**)

A 2.0-g. sample of 1-benzyl-4-(hydroxyacetyl)pyridine (**27**) dissolved in 50 ml. of absolute ethanol was hydrogenated with 0.5 g. of 10% palladium on charcoal catalyst (50 psi, 25°) for 16 hours. After filtering and concentration to remove solvent there remained 1.3 g. (100%) of 1-(4-piperidyl)-1,2-ethanediol (**30**); colorless oil. Its infrared spectrum was identical with that of an authentic sample (8b).

The *hydrochloride* salt was prepared from 0.4 g. of the above sample of **30** in 10 ml. of tetrahydrofuran solution by passing in hydrogen chloride gas; prisms from 2-propanol (0.46 g., 92%) m.p. 153-156°, lit. (8b) m.p. 155-156°.

Anal. Calcd. for $C_7H_{16}ClNO_2$: C, 46.28; H, 8.88; Cl, 19.52; N, 7.71. Found: C, 46.33; H, 8.95; Cl, 19.59; N, 7.66.

With 1-benzyl-2-(hydroxyacetyl)piperidine (**25**) under similar conditions (1.5 hours), 1-(2-piperidyl)-1,2-ethanediol (**28**) was obtained as a viscous oil (100%); carbonyl absorption bands absent in the infrared spectrum; ν cm^{-1} (neat), 3350. The racemate of **28** is described as an oil, b.p. 120-123° (2 mm.) (8a).

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