on the basis of a calculation of the buffer capacity of the solutions used as compared to the quantity of dihydroresorcinol. Since it appeared that the buffering action was principally due to dihydroresorcinol and its salt, a mixture of 20.0 g (178 mmoles) of dihydroresorcinol and 7.5 g (89 mmoles) of sodium bicarbonate in 80 ml of water were heated under reflux 8 hr before the cooled solution was acidified and extracted with chloroform. The chloroform extracts were extracted with 5% sodium bicarbonate solution; the extracts were acidified, heated to boiling, decolorized with charcoal, filtered, and permitted to cool. Yellow crystals, 9.8 g (49%), collected and were recrystallized from 1 *N* hydrochloric acid to give colorless crystals, mp 95.5–97.5° (lit.[2] mp 98°), which show a tendency to darken while drying. The compound reacts with potassium permanganate in acetone and with bromine in chloroform–carbon tetrachloride, but does not give a color with ferric chloride in aqueous dioxane: ultraviolet, λ_{max}^{EtOH} 238 mμ (log ε 4.14), $\lambda_{max}^{5\%NaHCO_3}$ 242 (4.16), λ_{max}^{2NNaOH} 397 (*ca.* 4.7); nmr (τ values, in $CDCl_3$, integral in parentheses), −0.56 (*ca.* 1), −COO*H*, shifting upfield with addition of dioxane; 4.05 (0.96), vinyl H; 6.62 (2.04), 6-protons; 7.26–7.72 (8.00), 2,4,4′- and 6′-protons; and 7.92–8.23 (3.96), 3,5′-protons.

The **p-bromophenacyl ester** was prepared from 0.50 g (2.2 mmoles) of dimer and 0.64 g (2.3 mmoles) of *p*-bromophenacyl bromide in the usual manner.[9] Recrystallization from aqueous ethanol gave light green crystals, mp 103.5–104.5°.

Anal. Calcd for $C_{20}H_{21}BrO_5$: C 57.02; H, 5.02; mol wt, 421. Found: C, 56.84; H, 5.07; mol wt, 426 (vapor pressure osmometer).

2-(3-Ketocyclohexenyl)cyclohexane-1,3-dione (3 ⇌ 10).—Preparation of the dehydrated dimer followed the method of Stetter, except that recrystallization was effected by dissolving the compound in chloroform and inducing crystallization by dilution with dioxane: mp 151–155° (lit.[2] mp 155°) with darkening; ultraviolet, λ_{max}^{EtOH} 268 mμ (log ε 4.14), λ_{sh} 236 (4.06), $\lambda_{max}^{6NH_2SO_4}$ 273 (4.19), λ_{sh} 242 (4.09), $\lambda_{max}^{H_2O}$ 284 (4.21) and 239 (4.07), $\lambda_{max}^{NaHCO_3 \text{ or } NaOH}$ 286 (4.34) and 238 (4.04); nmr, −0.21 (*ca.* 1), enol H, shifting upfield upon addition of dioxane; 4.06 (0.88), vinyl H; 7.46–7.56 (8.05, a rough doublet), 4,6,4′,6′-protons; 7.88–7.96 (4.09, a rough doublet), 5,5′-protons. The neutralization equivalent was determined to be 202 *vs.* the phenolphthalein end point (theory 206).

2-(3-Ketocyclohexyl)cyclohexane-1,3-dione (4 ⇌ 11).—Hydrogenated dehydrated dimer was prepared by hydrogenation of the dehydrated dimer with Pd–C in glacial acetic acid at 3 atm of hydrogen pressure. The product, after removal of the catalyst and acetic acid, was crystallized from ethyl acetate: mp 166.5–167.5° (lit.[2] mp 168°); ultraviolet, λ_{max}^{EtOH} 264 mμ (log ε 4.21), λ_{max}^{6NHCl} 278 (4.39), λ_{max}^{2NNaOH} 290 (4.40); nmr, 4.55 (enolic –OH, shifting to higher field upon addition of dioxane), 6.82 (H at 2), 7.33–7.83, 7.83–8.37, and 8.37–8.75. The integration suggested the presence of a mixture of **4** and **11** in the nmr sample.

Determination of pK_a.—Sorensen's glycine–NaOH buffer[10] was used in the determination of the pK_a of dimer and hydrogenated dehydrated dimer and citrate buffers[10] for the determination of the pK_a of dehydrated dimer. For dimer, optical densities at 397 mμ were plotted *vs.* pH, and the pH of half-development of the maximum absorption was found to be 10.8.

For dehydrated dimer, plots of optical density *vs.* pH at 263 and 286 mμ were made and found to have inflection points at 4.35 and 4.52 pH units, respectively. An average value of 4.4 is taken as the pK. A plot of the ratio of optical density at 260 to that at 270 *vs.* H_0 of a series of different concentrations of hydrochloric acid gave a barely defined inflection at H_0 −1.3 for the dehydrated dimer conjugate acid.

Since the buffer range of glycine–sodium hydroxide buffer did not extend to acidic enough solutions to define a whole titration curve, the pK_a of hydrogenated dehydrated dimer was calculated[6] on the observed absorbances at 266 and 288 mμ at three pH values. The mean of the pK values so calculated was 8.25 ± 0.07 (average deviation).

Acknowledgment.—The National Institutes of Health (GM 11013) provided financial support; the A-60 nmr spectrometer was purchased with the aid of an equipment grant from the National Science Foundation. Mr. Kenneth Wolma prepared samples of dimer and did some exploratory work on its structure.

(9) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, John Wiley and Sons, Inc., New York, N. Y., 1956, p 200.

(10) "International Critical Tables," Vol. I, McGraw-Hill Book Co., Inc., New York, N. Y., 1926, pp 82, 83.

Systems with Bridgehead Nitrogen. β-Ketols of the 1-Azabicyclo[2.2.2]octane Series

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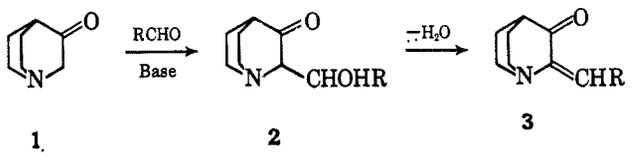
The preparations and chemical behavior of the first β-ketols incorporating the 1-azabicyclo[2.2.2]octane ring are described. Three different structural types are represented in this study. Methylolation of 3-quinuclidinone (**1**) with excess formaldehyde (potassium carbonate catalyst under appropriate conditions) led to 2,2-bismethylol-3-quinuclidinone (**4**) or 2-methylene-3-quinuclidinone (**3c**). 2-Methylol-3-quinuclidinone (**2c**) was prepared by hydration of **3c** cation. Starting with 4-acetylpiperidine and its N-benzyl derivative, syntheses of 4-hydroxymethyl-3-quinuclidinone (**17**) and 4-acetyl-3-quinuclidinol (**26**) were achieved. The bridgehead methylol compound **17** was found to be extremely stable whereas **26** underwent facile retrograde aldolization in basic media. The bismethylol derivative (**4**) readily loses one methylol group in base leading to ketol **2c**, which dehydrates with extreme ease rather than undergo demethylolation.

Although numerous derivatives of 1-azabicyclo[2.2.2]octane (quinuclidine) are known, none incorporating a β-ketol structure appear to have been described previously.[1] 3-Quinuclidinone (**1**) has been condensed with benzaldehyde[2,3] and quinoline-4-carboxaldehyde[3] to produce α,β-unsaturated ketones **3a** and **3b**, respectively. However, the β-ketol precursors **2a** and **2b** have not been isolated. In the present study three β-ketols of the quinuclidine series, each of a different type (including **2c**, R = H), have



1 **2** **3**

a, R = C_6H_5
b, R = 4-quinolyl
c, R = H

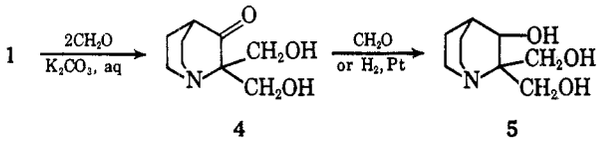
(1) (a) W. L. Mosby, "Heterocyclic Systems with Bridgehead Nitrogen," Part 2, Interscience Publishers, Inc., New York, N. Y., 1961, pp 1331–1356; (b) A. T. Nielsen and W. J. Houlihan, *Org. Reactions*, in press.

(2) V. Braschler, C. A. Grob, and A. Kaiser, *Helv. Chim. Acta*, **46**, 2646 (1963).

(3) G. R. Clemo and E. Hoggarth, *J. Chem. Soc.*, 1241 (1939).

been prepared and their chemical behavior examined and compared.

3-Quinuclidinone (**1**) has been condensed with formaldehyde under various conditions in the presence of potassium carbonate catalyst. A large excess of formaldehyde (20 mole equiv) was required to produce a 54% yield of 2,2-bismethylol-3-quinuclidinone (**4**) from **1** (aqueous, 52°, 1 hr). A parallel experiment

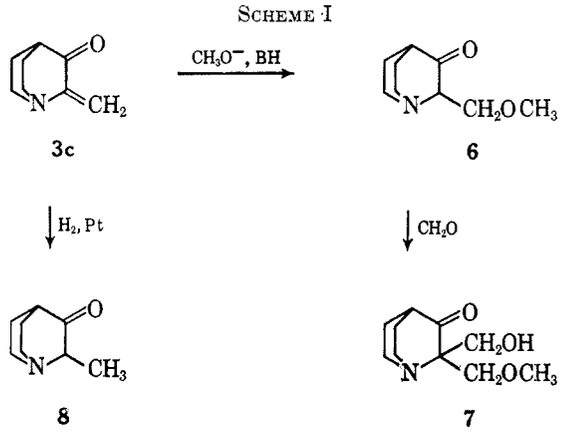


4 **5**

under only slightly more vigorous conditions (50–72°, 2 hr) produced a mixture of **4** (21%) and the triol, 2,2-bismethylol-3-quinuclidinol (**5**) (15%) by Cannizzaro reduction of **4**. Hydrogenation of **4** (platinum catalyst) in ethanol also led to **5**. Attempts to prepare ketol **2c** by direct methylolation of **1** were unsuccessful.

Employment of aqueous methanol as reaction medium and 5 mole equiv of formaldehyde (64°, 2 hr) produced 2-methoxymethyl-2-methylol-3-quinuclidinone (**7**) (16%): sharp methyl singlet (τ 6.6) in deuteriochloroform. This product reasonably arises from 2-methylene-3-quinuclidinone (**3c**) by methylolation of the methoxide adduct **6** (not isolated).[4]

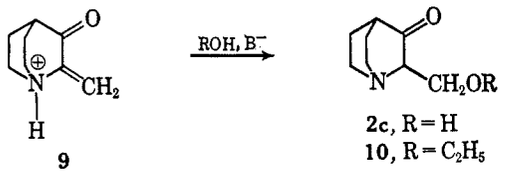
SCHEME I



3c **6** **8** **7**

2-Methylene-3-quinuclidinone (**3c**) (Scheme I) was prepared by reaction of **1** with formaldehyde (5 mole equiv, aqueous methanol, 60°, 5 hr). The compound, a light yellow oil, mp 23–24°, was isolated by distillation and purified by glpc (54% yield). Its structure is supported by its spectra; vinyl doublet at τ 4.25, 4.8; ν 1960 (C=O) and 1620 (C=C) cm^{-1}; λ_{max}^{EtOH} 221.5 mμ, ϵ_{max} 8700. The ultraviolet spectrum is characteristic of an α-substituted α,β-unsaturated ketone [*e.g.*, $CH_2{=}C(CH_3)COCH_3$, λ_{max}^{EtOH} 218 mμ (ϵ_{max} 8300)].[5] No large bathochromic shift is produced by the α-amino group[6] since resonance forms involving a bridgehead double bond are disallowed.[3,7] Hydrogenation of **3c** in ethanol at 1 atm pressure (platinum, 25°) resulted in rapid absorption of 1 mole equiv of hydrogen to produce 2-methyl-3-quinuclidinone (**8**), isolated as its picrate derivative; a characteristic 6.5-cycle methyl doublet is observed in the nmr spectrum of **8**.

The β-ketol, 2-methylol-3-quinuclidinone (**2c**), although unavailable by acid- or base-catalyzed condensation of **1** with formaldehyde, was prepared by hydration of 2-methylene-3-quinuclidinone cation (**9**) in 0.5 *N* hydrochloric acid. Ethanol also added readily



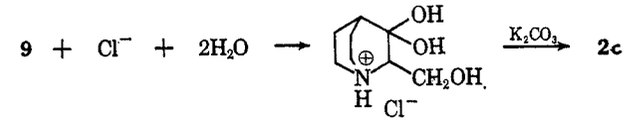
9

2c, R = H
10, R = C_2H_5

to **9**; ethanolic picric acid instantly precipitated the picrate of 2-ethoxymethyl-3-quinuclidinone (**10**); ν 1730 cm^{-1}, hydroxyl absorption absent. The combined electron-withdrawing effects of adjacent ammonium and carbonyl groups in **9** cause the olefinic double bond to behave as a very reactive nucleophilic acceptor. In the hydrochloride salt of **2c** the electron-withdrawing effects of α-ammonium and methylol groups combine similarly to activate the carbonyl group, since the salt crystallizes from water as the ketone hydrate (carbonyl absorption absent in its infrared spectrum).[8] The free base (**3c**) is not abnormally reactive since **2c** failed to form in aqueous or ethanol solution in the absence of added catalyst. A dilute solution of **3c** in ethanol was stable (no change in absorption intensity of the 221.5-mμ maximum during 24 hr); addition of acid resulted in immediate disappearance of the maximum which failed to return on making the solution basic (**3c** → **9** → **10** cation → **10**).

The behavior of ketols **2c** and **4** in basic and acidic media was examined. The bismethylol derivative (**4**) readily lost one methylol group on warming in 0.1 *N* aqueous sodium hydroxide solution, followed by rapid dehydration of the intermediate ketol **2c** to 2-methylene-3-quinuclidinone (**3c**). Evidently the base-catalyzed dehydration of **2c** is much more rapid than its demethylolation and the equilibrium in base does not favor **2c**. Complete demethylolation of **4** to 3-quinuclidinone (**1**) could not be realized under a variety of conditions. The low concentration of **2c** in reaction mixtures of **1** and formaldehyde, which accounts for its abortive isolation, thus results from its facile dehydration to **3c** and methylolation to **4**;[9] the unreac-

(8) A compound described as "2-methylene-3-quinuclidinone hydrochloride dihydrate" is available from the Aldrich Chemical Co., Inc., Milwaukee, Wis. (Item No. M4612-8, Catalog 12, 1966). However, to our knowledge, no mention of this compound has yet appeared in the chemical literature. The infrared spectra and a mixture melting point determination show the Aldrich sample and **2c** hydrochloride hydrate to be identical, *i.e.*, 3,3-dihydroxy-2-methylolquinuclidine hydrochloride (i). Potassium carbonate solution liberates the ketol **2c** from i.



i

(9) In general, the methylolation of active methylene compounds often proceeds to completion, since introduction of the second methylol group proceeds more rapidly than the first and the equilibrium appears to favor the more highly methylolated product: Y. Ishikawa and T. Minami, *Kogyo Kagaku Zasshi*, **63**, 277 (1960); *Chem. Abstr.*, **56**, 2322 (1962). An excess of ketone is required to secure reasonable yields of monomethylol compound.

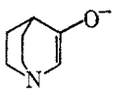
(4) β-Alkoxy ketones have been isolated as products of addition of alcohols to α,β-unsaturated ketones in the course of base-catalyzed aldol condensations (alcohol or aqueous alcohol solvent): A. T. Nielsen, D. W. Moore, and K. Highberg, *J. Org. Chem.*, **26**, 3691 (1961); S. G. Powell and W. J. Wasserman, *J. Am. Chem. Soc.*, **79**, 1934 (1957).

(5) K. Bowden, E. A. Braude, and E. R. H. Jones, *J. Chem. Soc.*, 948 (1946).

(6) K. Bowden and E. A. Braude, *ibid.*, 1068 (1952).

(7) B. M. Wepster, *Rec. Trav. Chim.*, **71**, 1159 (1952).

tivity of **1** is also involved.[2,3] Low ratios of formaldehyde to **1** (1:1 to 5:1), with reaction conditions designed to produce **2c**, led principally to recovered **1**. The relative unreactivity of **1** in the aldol condensation may be due to strain in its enolate ion (**1a**).[9,10] Con-



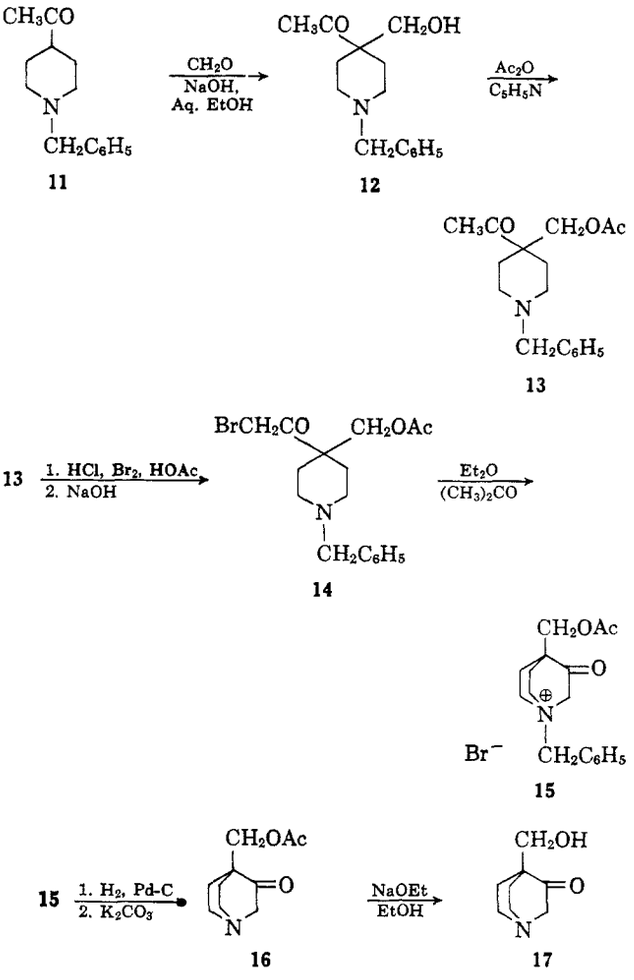
1a

tributing to the unreactivity of **2c** in the retroaldol condensation (relative to the competitive dehydration of **3c**) may be the strain in its enolate anion. In contrast to the facile degradation of the bismethylol derivative **4** in basic media, it was unaffected by heating in 0.2 *N* hydrochloric acid, and ketol **2c** could be recovered from 0.5 *N* hydrochloric acid after 16 hr at room temperature. Attempts to methylolate **1** in aqueous hydrochloric acid were unsuccessful.

A remarkable finding was that ketol **2c** underwent spontaneous dehydration to 2-methylene-3-quinuclidinone (**3c**) in an aprotic solvent. A sample of **2c** in deuteriochloroform on standing at room temperature for 9 days exhibited nmr and infrared spectra of **3c**. The rather basic quinuclidine nitrogen evidently catalyzes the dehydration even in an aprotic solvent (nonsolvent anion general base catalysis).[11] The process may be intramolecular, but does not involve a "heterocinchonine rearrangement" to 1-aza[3.2.2]-bicyclo-2-nonen-4-one.[2]

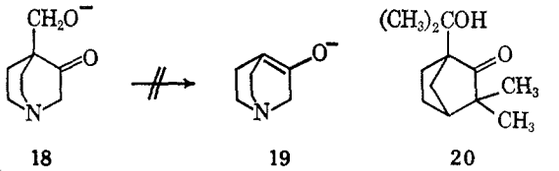
In contrast to the instability of β-ketols **2c** and **4** exhibited in basic media, the bridgehead hydroxymethyl β-ketol, 4-hydroxymethyl-3-quinuclidinone (**17**), is extremely stable. Its synthesis was achieved by reaction sequence **11** → **17** (Scheme II). Condensation of N-benzyl-4-acetylpiperidine (**11**)[12] with 1 mole equiv of formaldehyde in aqueous ethanolic sodium hydroxide produced 1-benzyl-4-acetyl-4-methylolpiperidine (**12**) by attack at the ring position. This result, rather than methyl attack, would be expected from reported behavior of formaldehyde in aldol condensations with other unsymmetrical methyl ketones in aqueous medium where condensation was found to occur on the most substituted α-carbon.[13] It was found convenient to acetylate the crude methylolation product, without isolation, to prepare the acetate **13**. Structure **13** is supported by the nmr spectrum; acetyl and acetate methyl singlets are found at τ 7.97 and 8.13 and methylene singlets of the benzyl and methyleneoxy groups at τ 6.00 and 6.67. The over-all yield of **13** from **11** was 37%. The acetate hydrochloride was brominated in acetic acid solution to yield, ultimately, 1-benzyl-4-acetoxymethyl-4-bromoacetylpiperidine (**14**) which in ether–acetone solution very rapidly cyclized[14] to 1-benzyl-4-acetoxymethyl-3-quinuclidinone bromide (**15**), isolated as the monohydrate in an over-all yield

SCHEME II



of 29% from **13**. Debenzylation of **15** by hydrogenation with palladium-on-charcoal catalyst, followed by neutralization of the hydrobromide intermediate, led to a quantitative yield of the acetate **16** which was readily converted into ketol **17** by ethoxide-catalyzed ester exchange; the over-all yield of **17** from **15** was 86%. Structure **17** is supported by the nmr spectrum (hydroxymethyl methylene singlet at τ 6.62); the remainder of the spectrum, except for the absence of the characteristic bridgehead hydrogen quintet centered at τ 7.80, is similar to that of 3-quinuclidinone.

As a β-ketol, 4-hydroxymethyl-3-quinuclidinone (**17**), mp 110–111°, exhibits remarkable stability in basic media. It may be recovered unchanged after 17 hr heating at 90° in 1 *N* sodium hydroxide solution. It, and its hydrochloride as well, sublimes on heating at atmospheric pressure without decomposition. The behavior is in agreement with a highly strained enolate ion intermediate (**19**) required of the retrograde aldol



condensation from the ketoalkoxide intermediate **18** and contrasts with the stability of the relatively less strained anion **1a** arising from **1**.[10] Similarly, no thermal deketolization of β-ketol **20** (stable up to 350°)

(10) The strain in 3-quinuclidinone enolate ion (**1a**) (derived by proton removal at the 2-position) relative to the desethylene monocyclic anion (derived analogously from 3-piperidone) may be estimated at *ca.* 1 kcal from the relative stabilities of bicyclo[2.2.2]octene and cyclohexene: R. B. Turner, W. R. Meador, and R. E. Winkler, *J. Am. Chem. Soc.*, **79**, 4116 (1957).

(11) C. D. Gutsche, R. S. Buriks, K. Nowotny, and H. Grassner, *ibid.*, **84**, 3775 (1962).

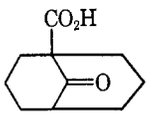
(12) A. T. Nielsen, D. W. Moore, J. H. Mazur, and K. H. Berry, *J. Org. Chem.*, **29**, 2898 (1964).

(13) J.-E. Dubois, *Ann. Chim.* (Paris), **6**, 406 (1951).

(14) T. D. Perrine, *J. Org. Chem.*, **22**, 1484 (1957).

is observed because the required highly strained enol intermediate cannot form.[15,16]

Strained bridgehead enol intermediates prohibit or render difficult decarboxylation of β-keto acids having a carboxyl group at the bridgehead.[17] The effect of structure on the ease of decarboxylation (intermediate enol formation) has been explained in terms of the degree of overlap between the developing carbanion and the carbonyl group.[17] In **17** the dihedral angle between the methylol group and carbonyl group is zero (measured from Dreiding models) so that the developing carbanion achieves no stabilization by overlap with the π electrons of the adjacent carbonyl group. The situation is analogous to that of 9-oxobicyclo[3.3.1]nonane-1-carboxylic acid (**21**) which does not decarboxylate when heated to 250°.[18]

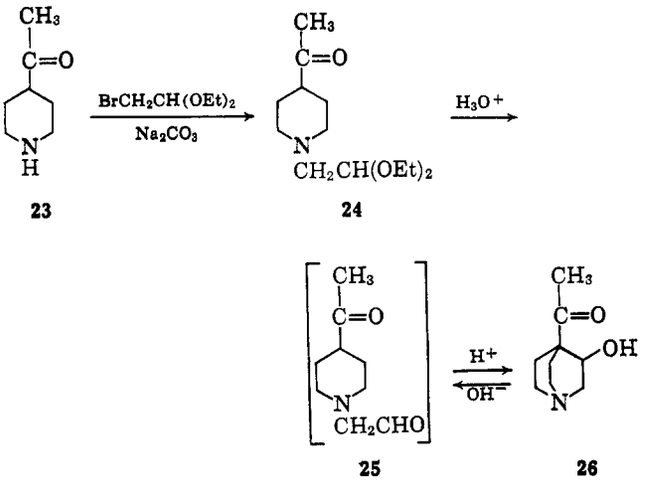


21

The mechanism of the retrograde aldol condensation has been studied.[19-22] Contrary to the earlier conclusions of Nelson and Butler[19]—that the initial step is a slow proton removal, followed by a rapid cleavage to enolate anion—there now appears to be general agreement[20-22] based on kinetic evidence that the initial step is fast and involves specific solvent anion base catalysis leading to a ketoalkoxide intermediate (*e.g.*, **18**). The following step in the process is described as a slow rate-determining dissociation into enolate ion and carbonyl compound. Our results are in agreement with this mechanism since the slow step leading to the enolate ion **19** would involve loss of formaldehyde from anion **18**.

A third type of β-ketol in the 1-azabicyclo[2.2.2]-octane series has been prepared employing an intramolecular aldol condensation in the ring-closure step.[23] 4-Acetyl-3-quinuclidinol (**26**) was obtained in 10% yield by an intramolecular aldol condensation (in 0.6 *N* hydrochloric acid) of the keto aldehyde **25** (not isolated) which is formed *in situ* from its acetal, 4-acetyl-1-(2,2-diethoxyethyl)piperidine (**24**). Acetal **24** was prepared from 4-acetylpiperidine (**23**)[12] and bromoacetaldehyde diethyl acetal. Unlike **17**, β-ketol **26** is very sensitive to bases and is destroyed by warming with aqueous 1 *N* sodium hydroxide solution. Basic catalysts were ineffective in cyclizing **25** (liberated from its hydrochloride salt) to **26**. The nmr spectrum of **26** is in agreement with its structure; singlet methyl peak at τ 7.87. Thus the possibility is excluded that intramolecular aldol condensation occurred on the methyl group to form 3-hydroxy-5-oxo[4.2.2]bicyclodecane.

(15) T. Mole, *Chem. Ind.* (London), 1164 (1960).
(16) G. G. Smith and B. L. Yates, *J. Org. Chem.*, **30**, 2067 (1965).
(17) J. P. Ferris and N. C. Miller, *J. Am. Chem. Soc.*, **85**, 1325 (1963).
(18) A. C. Cope and M. E. Synerholm, *ibid.*, **72**, 5228 (1950).
(19) W. E. Nelson and J. A. V. Butler, *J. Chem. Soc.*, 957 (1938).
(20) Y. Pocker, *Chem. Ind.* (London), 89 (1959).
(21) J. C. Speck and A. A. Forist, *J. Am. Chem. Soc.*, **79**, 4659 (1957).
(22) M. R. F. Ashworth and J.-E. Dubois, *Bull. Soc. Chim. France*, 147 (1955).
(23) Similar ring closures have been employed in the carbocyclic series; *cf.* R. W. Guthrie, A. Philipp, Z. Valenta, and K. Wiesner, *Tetrahedron Letters*, 2945 (1965).



An unsuccessful attempt was made to employ the Mannich reaction—with 4-acetylpiperidine (**23**)—as a ring-closure process leading to 4-acetyl-1-azabicyclo-[2.2.1]heptane or 4-oxo-1-azabicyclo[3.2.2]nonane. Reaction of 4-acetylpiperidine hydrochloride with formaldehyde led to a quantitative conversion to bis(4-acetyl-1-piperidyl)methane (**27**). Molecular weight, neutral equivalent, absence of hydroxyl absorption in the infrared region, and sharp acetyl methyl (τ 7.85) and $-NCH_2N$ methylene (τ 7.1) singlet peaks in the nmr spectrum support assignment of structure **27**. Although the Mannich reaction has been successfully employed in ring closure reactions,[24] the transition states leading to product from the Mannich intermediate (immonium ion) in these known examples is strain free; much strain would be developed, at the site of the developing nitrogen bridgehead, in the transition state leading to bicyclic products from 4-acetylpiperidine in the Mannich reaction.

Experimental Section[25]

2,2-Bismethylol-3-quinuclidinone (4).—A solution of 16.2 g (0.1 mole) of 3-quinuclidinone hydrochloride and 15 g of anhydrous potassium carbonate in 150 ml of formalin (2.0 moles of formaldehyde) was heated in a water bath at 52 ± 4° for 1 hr. After cooling, the solution was saturated with potassium carbonate and extracted successively with four 80-ml portions of methylene chloride. The combined extracts were dried and solvent was removed by distillation. The residue, contained in an open flask, was heated on the steam bath with 500 ml of heptane for 1 hr; the hot heptane extract was then decanted and discarded. The residue was heated to boiling in the same manner with 500 ml of benzene for 8 hr, additional benzene being added at intervals to replace that lost by evaporation. During the heating paraformaldehyde collected on the upper walls of the flask and some gummy solid separated. The mixture was filtered and the filtrate concentrated to yield 19.6 g of residue which was extracted first with 300 ml of boiling heptane, then with 400 ml of boiling benzene. On cooling, the heptane extract deposited 0.8 g of diol **4**, mp 141–145°, and the benzene extract gave 6.3 g, mp 141–145°. A second crop was isolated from the benzene mother liquor, 2.9 g, mp 143–146°; total yield, 10.0 g (54%). A parallel run at 60 ± 3°, 0.5 hr, gave a 40% yield of **4**, mp 142–146°; lower molar ratios of formaldehyde gave lower yields. Recrystallization from benzene gave chunky prisms: mp 146–

(24) G. de Stevens, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.), **23**, 105 (1962).
(25) Melting points were determined on a Kofler hot stage and are corrected. Infrared spectra were determined on a Perkin-Elmer Model 137 spectrophotometer, nmr spectra on a Varian-A-60 spectrometer with pure liquids or 10–20% solutions. Ultraviolet spectra were determined on a Cary Model 14 spectrophotometer. Magnesium sulfate was employed as a drying agent.

147°; ν 1710, 3300 cm^{-1} (Nujol mull); τ^{CDCl_3} 6.0 singlet (two methylenes), 6.2 singlet (two hydroxyls).

Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56; mol wt, 185.22. Found: C, 58.66; H, 8.18; N, 7.53; mol wt, 186.

A **picrate** derivative was prepared in ethanol; long yellow prisms, mp 225–227° dec, from ethanol.

Anal. Calcd for $C_{15}H_{18}N_4O_{10}$: C, 43.48; H, 4.38; N, 13.52. Found: C, 43.25; H, 4.29; N, 13.54.

A 200-mg sample of **4** in 2 ml of 0.1 *N* aqueous sodium hydroxide solution was heated at 72° for 1 hr. The pale yellow solution was saturated with potassium carbonate and extracted with methylene chloride. After drying and removing the solvent there remained 140 mg of oil, 80 mg of which was soluble in 25 ml of boiling ether; 30 mg of the ether-soluble material was soluble in 25 ml of boiling hexane and had an infrared spectrum identical with that of 2-methylene-3-quinuclidinone **3c**; picrate derivative, mp 140–144° [melting point undepressed when mixed with authentic sample prepared from **3c**, mp 142–144°; derivative actually that of 2-ethoxymethyl-3-quinuclidinone (see below)].

2,2-Bismethylol-3-quinuclidinol (5). A. From 3-Quinuclidinone.—A solution of 1.62 g (0.01 mole) of 3-quinuclidinone hydrochloride, 3 g of anhydrous potassium carbonate in 15 ml of formalin (0.20 mole of formaldehyde), and 10 ml of water was heated at 50–72° for 2 hr. After cooling, the residue was extracted with methylene chloride; the extracts were dried and concentrated. Fractional crystallization of the residue from heptane led to 0.46 g (21%) of crude 2,2-bismethylol-3-quinuclidinone (**4**), mp 120–140°. Crystallization of the remainder from benzene gave 0.33 g (15%) of crude 2,2-bismethylol-3-quinuclidinol (**5**), mp 152–168°; recrystallization from chloroform gave 0.12 g, mp 170–172°, with softening near 155–160°. Further recrystallization from chloroform gave small needles, mp 171–172°. When mixed with an authentic sample, mp 170–172°, prepared from **4**, the melting point was not depressed.

B. From 2,2-Bismethylol-3-quinuclidinone (4).—A solution of 1.85 g (0.01 mole) of 2,2-bismethylol-3-quinuclidinone (**4**) in 40 ml of ethanol was hydrogenated in a Parr apparatus with 0.3 g of platinum oxide catalyst (53 psi, 25°) until hydrogen uptake was complete (1 hr, 1.0 mole equiv). The mixture was filtered and concentrated to dryness to yield 1.85 g of crude triol **5**, mp 157–160°. Recrystallization from chloroform gave needles (1.2 g, mp 170–172°, with softening near 155–160°); ν 3400 cm^{-1} (OH), C=O absorption absent (Nujol).

Anal. Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48; mol wt, 187.23. Found: C, 57.83; H, 9.11; N, 7.53; mol wt, 190.

2-Methoxymethyl-2-methylol-3-quinuclidinone (7).—A solution of 16.2 g (0.1 mole) of 3-quinuclidinone hydrochloride, 16 g of anhydrous potassium carbonate, 36.6 ml of formalin (0.5 mole of formaldehyde), and 75 ml of water in 200 ml of methanol was heated in a water bath at 64 ± 4° for 2 hr. The solution was concentrated *in vacuo* to remove methanol; the aqueous residue was saturated with potassium carbonate and extracted five times with methylene chloride. The extracts were dried and concentrated; the residue was extracted six times with 250-ml portions of hexane. The combined extracts were cooled to room temperature and decanted from a gum which separated. On seeding, the decantate deposited 2.0 g of **7**, mp 106–112°. From the mother liquor, by concentration and extraction with hot cyclohexane, there was obtained an additional 1.2 g, mp 107–114°; total yield, 3.2 g (16%). Recrystallization from cyclohexane gave prisms: mp 115–116°; ν 3050 (OH) and 1700 (C=O) cm^{-1}; nmr spectrum ($CDCl_3$), sharp methyl singlet (τ 6.6), methylene multiplet centered at τ 6.1 (4), and hydroxyl singlet at τ 6.2 (1).

Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03; mol wt, 199.24. Found: C, 60.22; H, 8.63; N, 7.01; mol wt, 203.

2-Methylene-3-quinuclidinone (3c).—A solution of 16.2 g (0.1 mole) of 3-quinuclidinone hydrochloride, 18 g of anhydrous potassium carbonate, 36.6 ml of formalin (0.5 mole of formaldehyde), and 50 ml of water in 150 ml of methanol was heated in a water bath at 60 ± 2° for 5 hr. The mixture was concentrated to near dryness; the residue was extracted three times with methylene chloride. The extracts were dried and solvent was removed by concentration *in vacuo* to yield 17.0 g of yellow oil. Distillation through a short still head (oil bath temperature 155–175°) during 2 hr resulted in slow distillation of a light yellow oil, 9.7 g, bp 45–85° (1–15 mm); a brown residue, 3.40 g, remained. Purification of the distillate by glpc on a 20 ft × 0.5 in. Chromosorb W column packed with fluorosilicone FS1265-QF-1 (20%) and Dowfax 9N9 (1%) (189°, flow rate 145 cc/min) gave 76% 2-methylene-3-quinuclidinone (retention time 16.3 min), 14% 3-quinuclidinone (retention time 18.5 min), and 10% of an unidentified component (2-min retention time). The conversion of **1** to **3c** was 54% (63% yield based on unrecovered 3-quinuclidinone). A sample of **3c** purified by chromatography was distilled, bp 94–95° (1.4 mm), $n^{25}D$ 1.5120, mp 23–24°; chromatographic analysis indicated a purity of 98% (3-quinuclidinone, 2%). The infrared spectrum of **3c** (neat) revealed strong bands at 1690 (C=O) and 1620 (C=C) cm^{-1}; ultraviolet λ_{max} 219 mμ (ϵ_{max} 8500) in hexane, 221.5 mμ in 95% ethanol (ϵ_{max} 8700). The nmr spectrum ($CDCl_3$) revealed vinyl protons (2) doublet at τ 4.25, 4.8, bridgehead proton (1) quintet centered at τ 7.4; the four α protons appeared as a multiplet centered at τ 6.9 and the β protons as a multiplet centered at τ 8.0.

Anal. Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21; mol wt, 137.18; neut equiv, 137.18. Found: C, 69.88; H, 8.11; N, 10.18; mol wt, 140; neut equiv, 138.

A **picrate** derivative was prepared in ethanol solution; flat, yellow prisms, mp 142–144° after recrystallization from ethanol. Its elemental analysis and infrared spectrum (ν 1725 cm^{-1}, hydroxyl band absent) suggest that addition of ethanol to the olefinic double bond of **3c** occurred leading to the picrate derivative of **2-ethoxymethyl-3-quinuclidinone (10)**.

Anal. Calcd for $C_{16}H_{20}N_4O_9$: C, 46.60; H, 4.89; N, 13.59. Found: C, 46.58; H. 4.98; N, 13.71.

2-Methylene-3-quinuclidinone (82.5 mg) in 15 ml of ethanol was hydrogenated with platinum oxide catalyst (51.7 mg) at 25°, 706 mm; 1 mole equiv of hydrogen was absorbed in 10 min after which time hydrogen uptake proceeded more slowly. After 23 min (1.15 mole equiv of hydrogen absorbed) the mixture was filtered and the filtrate was concentrated to yield 80 mg of an oil containing mainly **2-methyl-3-quinuclidinone (8)**; strong carbonyl absorption at 1700 cm^{-1} (film) and a methyl doublet (J = 6.5 cps) in the nmr spectrum (τ 8.62, 8.75) measured in deuteriochloroform; vinyl peaks absent. The presence of some (*ca.* 15%) 2-methyl-3-quinuclidinol in the unpurified oily product was indicated by weak hydroxyl absorption in the infrared spectrum as well as by a second, weaker methyl doublet (τ 8.72, 8.85) in the nmr spectrum. A **picrate** of ketone **8** was prepared in ethanol: mp 225–226°; ν^{KBr} 1730 (C=O) cm^{-1}.

Anal. Calcd for $C_{14}H_{16}N_4O_7 \cdot 0.5C_2H_6O$: C, 46.04; H, 4.89; N, 14.32. Found: C, 46.48; H, 4.58; N, 14.84.

2-Methylol-3-quinuclidinone (2c).—A solution of 0.6 g of 2-methylene-3-quinuclidinone (**3c**) in 10 ml of 0.5 *N* hydrochloric acid was kept at room temperature for 16 hr. Some white solid (27 mg) was removed by filtration; the filtrate was saturated with potassium carbonate and extracted with methylene chloride; the extracts were dried and concentrated to yield 0.7 g of oil. The oil was extracted with 50 ml of warm heptane; chilling the extract in ice produced 0.143 g of flat prisms of **2c**, mp 46–48; recrystallization from heptane gave large flat prisms, mp 48–54°; ν^{Nujol} 3400 (OH), 1720 (C=O) cm^{-1}; nmr ($CDCl_3$), methylene multiplet (2 H) centered at τ 6.15; on standing at room temperature 9 days the colorless solution became yellow and exhibited peaks characteristic of a mixture of **2c** and 2-methylene-3-quinuclidinone (**3c**) (estimated 1:1 mixture). Unsuccessful attempts were made to isolate **2c** from reactions of 3-quinuclidinone with formaldehyde (potassium carbonate catalyst) employing various reactant ratios and reaction conditions.

Anal. Calcd for $C_8H_{13}NO_2$: C, 61.92; H, 8.44. Found: C, 61.81; H, 8.15.

Treatment of 2-methylene-3-quinuclidinone (**3c**) (0.14 g.) with 0.2 *N* hydrochloric acid (6 ml) deposited 0.13 g of crystalline **2c** hydrochloride hydrate[8]; recrystallization from water gave prisms, mp 271–273° (capillary). The infrared spectrum (Kel-F oil mull) showed strong hydroxyl stretching at 3200 cm^{-1}; carbonyl and olefinic absorption absent.

Anal. Calcd for $C_8H_{14}ClNO_2 \cdot H_2O$: C, 45.83; H, 7.69; Cl, 16.91; N, 6.68. Found: C, 45.86; H, 7.91; Cl, 17.20; N, 6.50.

Water is only partially removed by drying at 100° (0.1 mm) over phosphorus pentoxide for 15 hr. Found: C, 47.07; H, 7.59; Cl, 17.69; N, 6.86 (carbonyl absorption absent). A sample made basic with potassium carbonate solution produced 2-methylol-3-quinuclidinone (**2c**), mp 46–47°; infrared bands

at 3400 (OH) and 1720 cm^{-1} (C=O). A sample of "2-methylene-3-quinuclidinone hydrochloride dihydrate" (Aldrich Chemical Co., Catalog 12, 1966, Item No. M4612-8),[8] mp 272–273° (capillary) in our hands, was found to have the same infrared spectrum as that of **2c** hydrochloride hydrate (carbonyl and olefinic absorption absent); when mixed with our sample the melting point was not depressed.

1-Benzyl-4-acetyl-4-methylolpiperidine (12).—To a solution of 8.68 g (0.04 mole) of 1-benzyl-4-acetylpiperidine (**11**)[12] in 50 ml of 95% ethanol was added 10 ml of 0.1 *N* sodium hydroxide solution and 3.15 ml of formalin solution (0.042 mole of formaldehyde). The solution was allowed to stand at room temperature for 43 hr and then treated with 1 ml of glacial acetic acid. The mixture was then concentrated to remove volatile materials leaving 10.9 g of very viscous residue. Distillation of the crude product gave fractions (1) 3.3 g, bp 128–170° (0.8 mm), containing much unreacted **11**; (2) 5.7 g, bp 170–176° (0.9 mm), principally **12**; and (3) 1.1 g of residue. Trituration of fraction 2 with cold hexane gave 3.4 g of material, mp 77–89°; recrystallization from cyclohexane gave 3.1 g (31%) of **12**, mp 91–93°. A second recrystallization gave colorless flat prisms, mp 93–94°; infrared bands (KBr) at 3500, 3200 (OH), and 1700 (C=O) cm^{-1}. Piperidine was found to be an ineffective catalyst for the condensation.

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.86; H, 8.67; N, 5.70.

1-Benzyl-4-acetoxymethyl-4-acetylpiperidine (13).—For preparation of the acetate of **13** it was found convenient to employ the crude methylolation product directly. To the crude product (undistilled) of methylolation of 8.68 g (0.04 mole) of 1-benzyl-4-acetylpiperidine (obtained by the procedure described above) was added 40 ml of acetic anhydride and 100 ml of pyridine; the mixture was allowed to stand 40 hr at room temperature and then heated on the steam bath for 8 hr. The mixture was concentrated *in vacuo* to a volume of *ca.* 30 ml; the residue was diluted with 100 ml of water and treated with concentrated ammonia and ammonium acetate until the oily acetate derivative separated. The mixture was extracted twice with ether, and the extracts were dried and concentrated to yield 11.7 g of residue. Distillation gave fractions (1) 4.85 g, bp 120–157°, containing some recovered ketone (**11**); (2) 4.3 g (37%) of acetate **13**, bp 157–165° (0.4 mm), $n^{25}D$ 1.5155; and 1.1 g of residue. Fraction 2 revealed no infrared absorption near 3500 cm^{-1}, but strong carbonyl bands at 1740 and 1700 cm^{-1} (ester and ketone, respectively).

Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84; mol wt, 289.4; sapon equiv, 289.4. Found: C, 70.13; H, 7.97; N, 4.84; mol wt, 301; sapon equiv, 306.

1-Benzyl-4-acetoxymethyl-3-quinuclidinone Bromide (15).—A solution of 3.07 g (0.0107 mole) of 1-benzyl-4-acetoxymethyl-4-acetylpiperidine (**13**), bp 157–165° (0.4 mm), in 100 ml of ether was treated with dry hydrogen chloride to precipitate the hydrochloride salt. The ether was removed *in vacuo;* the residue was dissolved in 15 ml of acetic acid. Bromine, 1.71 g (0.0107 mole), was then added; the solution was allowed to stand until the bromine color had disappeared (2 hr). The solvents were removed by concentration *in vacuo;* the oily residue was dissolved in 40 ml of water by warming it slightly. Ether (40 ml) was added; the solution was made alkaline (pH *ca.* 12) by addition of 10% sodium hydroxide solution. The solution was extracted twice with ether; the extracts were concentrated to yield 3.8 g of crude **1-benzyl-4-acetoxymethyl-4-bromoacetylpiperidine (14)**; it was dissolved in 50 ml of acetone, 30 ml of ether added, and the mixture allowed to stand overnight at room temperature. White prisms of the cyclized product (**15**) slowly separated: 1.2 g (29%), mp 118–135°. A sample recrystallized from 95% ethanol, mp 112–118°, was employed for analysis: infrared bands (KBr), 3600–3400 and 1740 cm^{-1} (single strong peak).

Anal. Calcd for $C_{17}H_{22}BrNO_3 \cdot H_2O$: C, 52.85; H, 6.26; Br, 20.68; N, 3.63. Found: C, 52.95; H, 6.21; Br, 20.60; N, 3.59.

4-Hydroxymethyl-3-quinuclidinone (17).—A 3.42-g (0.00885-mole) sample of the bromide **15** monohydrate, mp 105–120°, dissolved in 100 ml of 50% aqueous ethanol was hydrogenated with 10% palladium-on-charcoal catalyst (1.0 g) (50 psi, 25°). The theoretical amount of hydrogen was absorbed during 15 min after which time hydrogen uptake ceased; the mixture was filtered and the filtrate was concentrated to dryness to yield 2.49 g (100%) of **4-acetoxymethyl-8-quinuclidinone hydrobromide.** The free base was liberated by treatment with saturated potassium carbonate solution and separated by extraction with methylene chloride to yield 1.73 g (99%) of **4-acetoxymethyl-3-quinuclidinone (16)** as a pale yellow oil; infrared, OH and NH bands absent; bands at 1750 cm^{-1} (acetate) and 1725 cm^{-1} (ketone). To the acetate (1.73 g) in 40 ml of absolute ethanol was added 0.1 g of sodium methoxide and the solution stored for 24 hr at room temperature. After concentrating to near dryness *in vacuo*, the residue was treated with saturated potassium carbonate solution and extracted with methylene chloride to yield 1.18 g (86%) of crystalline **4-methylol-3-quinuclidinone,** mp 103–106°. Recrystallization from cyclohexane gave long needles: mp 110–111°; infrared (KBr), 3100 (OH), 1720 (medium), and 1700 (strong) (carbonyl) cm^{-1}.

Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.92; H, 8.36; N, 8.90.

The ketol **17** is very stable in basic solutions. A 0.15-g sample dissolved in 2 ml of 1 *N* sodium hydroxide solution was heated at 90° for 17 hr. Addition of potassium carbonate followed by extraction with methylene chloride gave 0.1 g of recovered ketol, mp 90–100°, as the only neutral product. Heating a 0.4-g sample in 40 ml of water in the absence of added catalyst at 190° for 16 hr led principally to a black tar from which crystals of unchanged reactant, mp 100–106°, could be extracted with hot cyclohexane. The ketol may be sublimed at a bath temperature of 215° (1 atm) without decomposition, mp 108–110°. The hydrochloride, mp 265°, may also be sublimed at 1 atm (oil bath, 190–250°) without decomposition, mp 255–265°; infrared bands at 3400 and 1720 cm^{-1}.

4-Acetyl-1-(2,2-diethoxyethyl)piperidine (24).—A 3.81-g (0.03-mole) sample of 4-acetylpiperidine[12] in 30 ml of absolute ethanol was treated with 6.0 g of bromoacetaldehyde diethyl acetal and 1.6 g of powdered anhydrous sodium carbonate; the mixture was heated under reflux for 24 hr. The mixture was concentrated to near dryness, treated with saturated potassium carbonate solution, and extracted with ether three times. The combined ether extracts were dried and concentrated to yield 7.31 g (100%) of crude **24**, $n^{23.5}D$ 1.4548; its infrared spectrum was identical with a distilled sample. Distillation of a 2.48-g aliquot gave 1.84 g (76%) of pure **24**; bp 100–101° (0.5 mm), $n^{25}D$ 1.4581; infrared, 1720 (carbonyl) cm^{-1}; NH and OH bands present.

Anal. Calcd for $C_{13}H_{25}NO_3$: C, 64.16; H, 10.36; N, 5.76; mol wt, 243.34. Found: C, 64.37; H, 10.47; N, 5.76; mol wt, 233.

4-Acetyl-3-quinuclidinol (26).—A solution of 1.22 g (0.005 mole) of acetal **24** in 150 ml of 0.6 *N* aqueous hydrochloric acid solution was heated under reflux for 15 hr. The yellow solution was then concentrated to dryness, treated in the usual manner with saturated potassium carbonate solution, and extracted with methylene chloride to yield 0.63 g of oily free base. Extraction of this material with 50 ml of boiling cyclohexane gave, after cooling, 80 mg (10%) of 4-acetyl-3-quinuclidinol (**26**), mp 121–124°; recrystallization from cyclohexane gave prisms, mp 125–126°. The infrared spectrum (KBr) revealed strong bands at 3100 and 1700 cm^{-1}. The nmr spectrum ($CDCl_3$) revealed a methyl singlet at τ 7.87, hydroxyl singlet at τ 5.7, and multiplets of α and β hydrogens centered at τ 7.1 and 8.3, respectively, and resembled those found in the nmr spectrum of 3-quinuclidinol (τ 7.3 and 8.3 in the same solvent). The bridgehead multiplet at τ 6.25 found in 3-quinuclidinol was absent in the spectrum of **26**.

Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.9; N, 8.28; mol wt, 169.2. Found: C, 64.06; H, 9.05; N, 8.39; mol wt, 177.

Bis(4-acetyl-1-piperidyl)methane (27).—A 2.54-g (0.02-mole) sample of 4-acetylpiperidine[12] was neutralized with 1 *N* hydrochloric acid (methyl red indicator); the solution was diluted to 200 ml with water. Formalin (1.5 ml, 0.02 mole of formaldehyde) was added and the mixture was allowed to stand at room temperature for 21 hr. The solution was then heated on the steam bath for 2.5 hr and concentrated to near dryness *in vacuo*. Treatment with saturated potassium carbonate solution and methylene chloride in the usual manner gave 2.58 g (97%) of crude **27**, mp 45–49°. Recrystallization from heptane gave 1.69 g, mp 50–59°, and a second recrystallization gave 1.06 g of white flakes, mp 58–59°. In another parallel run (1-mmole scale) a 95% yield of sublimed product, mp 53–59°, was obtained. The substance gives a positive iodoform test. The infrared spectrum (KBr) revealed no OH or NH band and a strong carbonyl band at 1700 cm^{-1}.

Anal. Calcd for $C_{15}H_{26}N_2O_2$: C, 67.63; H, 9.84; N, 10.52; mol wt, 266.4; neut equiv, 133.2. Found: C, 67.44; H, 9.8; N, 10.67; mol wt, 273; neut equiv, 134.

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Bicyclic Bases. Synthesis of 2,5-Diazabicyclo[2.2.1]heptanes[1]

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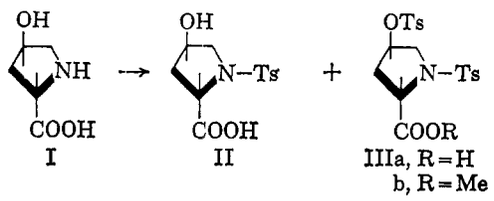
A route to the novel bicyclic system, 2,5-diazabicyclo[2.2.1]heptane, has been elaborated. The starting material, hydroxy-L-proline, was transformed to tritosylhydroxy-L-prolinol, which was then cyclized to 2-tosyl-5-benzyl-2,5-diazabicyclo[2.2.1]heptane with benzylamine. The latter structure was subsequently converted to the parent bicyclic system. Some of the reaction mechanisms leading to the bicyclic compound are discussed, and the nmr spectra of the title compound and its ditosyl derivative are interpreted.

The piperazine ring, which is capable of undergoing conformational inversion,[2] is encountered in a variety of medicinal agents. An approach to investigating the nature of conformational species which are reponsible for biological activity would involve constraining the piperazine ring in a single conformation. One such structure which fulfills the requirements of conformational rigidity is 2,5-diazabicyclo[2.2.1]heptane (XI). We wish to report on the synthesis of XI *via* a novel route which establishes the absolute configuration of this bicyclic system and, moreover, is of general utility in the preparation of other bicyclic structures which are not easily accessible by other methods.

The starting material for the synthesis is hydroxy-L-proline (I), whose absolute stereochemistry[3] is established. In the conception of the synthetic approach to XI, it was desirable to block the basic nitrogen of I with a protective group which would withstand the rigors of reactions employed in the synthetic sequence and also be capable of being removed without affecting other substituents in the molecule. The tosyl group fulfilled these requirements.

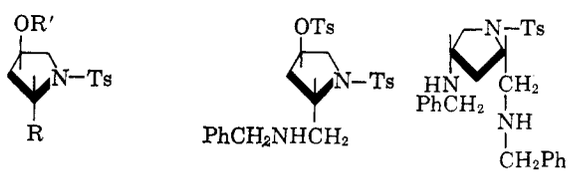
Hydroxy-L-proline (I) was tosylated in aqueous sodium hydroxide solution to afford, in high yield, a mixture of the expected N-tosyl derivative (II) and N,O-ditosylhydroxy-L-proline (IIIa). The identity of IIIa was determined by converting this compound to N,O-ditosylhydroxy-L-proline methyl ester (IIIb). The



same compound[4] was also prepared by tosylation of IV in pyridine solution. The yield of IIIa was increased at the expense of the major product when the reaction time was lengthened. It was found that II could be transformed to IIIa by prolonged exposure to tosyl chloride in aqueous sodium hydroxide solution. Hence, under the experimental conditions, N-tosylation occurred rapidly and this was followed by slow O-tosylation.

Treatment of II with diazomethane gave the methyl ester (IV) which was then reduced to N-tosylhydroxy-L-prolinol (V). It was found that reduction with lithium borohydride produced the highest yield. Attempts to reduce the acid (II) or ester (IV) with lithium aluminum hydride afforded V in much lower yield. Tosylation of V in pyridine solution gave the tritosyl derivative VI. The *trans* stereochemistry of this key intermediate is essential for the subsequent ring closure step since it was expected that displacement of the primary tosyloxy group by an amine nucleophile should produce the transient intermediate, VII, which would then undergo ring closure by internal SN2 expulsion of the secondary tosyloxy substituent.

The desired 2,5-diazanorbornane derivative (IX) was obtained in 86% yield by refluxing a toluene solution containing 3 equiv of benzylamine and 1 equiv of intermediate VI. Two equivalents of benzylamine acted as a proton acceptor for *p*-toluenesulfonic acid formed in the reaction. Significantly, no compounds corresponding to VII and VIII could be detected in the reaction mixture after approximately 50% of VI had been converted to IX. This suggests that displacement of the primary tosyloxy group by benzylamine proceeds in a rate-determining step to give intermediate VII which then rapidly cyclizes to IX.



IV, R = COOMe; R′ = H
V, R = CH_2OH; R′ = H
VI, R = CH_2OTs; R′ = Ts

VII VIII

In preliminary experiments, N-tosylpiperidine was employed as a model compound to explore the possibility of reductively cleaving the tosyl group in IX by treatment with sodium in liquid ammonia.[5] However, since this method gave yields of piperidine which were not greater than 30%, a more drastic procedure

(1) This investigation was supported in whole by Public Health Service Grant GM 09402 from the Institute of General Medical Sciences.

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(5) Reference 3, Vol. 2, p 1239.