Azabicyclic Alcohols. V. Synthesis and Stereochemistry of the 1-Azabicyclo[3.2.1]octanols

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Both epimers of the 1-azabicyclo[3.2.1]octan-3-, -4-, and -6-ol isomers have been synthesized and their stereochemistry has been assigned. The alcohols were obtained by reductions of their corresponding ketones, except for the *exo*-6-hydroxy isomer, which was obtained by Raney nickel catalyzed epimerization of the *endo* isomer, or (together with its epimer) by cyclodehydration of 3-piperidylethylene glycol. Attempts to prepare this *exo* alcohol by oxidative epimerization of the *endo* isomer were unsuccessful. Unexpectedly, several condensation products with the oxidized solvent were formed. Structures of two of these products have been assigned as 7-ethylidene- and 7-ethyl-1-azabicyclo[3.2.1]octan-6-ols (**15** and **16**), respectively.

We have been investigating the synthesis and stereochemical correlations of pharmaceutically useful azabicyclic alcohol epimers. Previous papers in this series have discussed fused bicyclic, bridgehead nitrogen systems.[1] We now report the results of a study of the 1-azabicyclo[3.2.1]octanols, a bridged bicyclic system that differs from its fused analogs in that inversion of the nitrogen atom is no longer possible. Apart from presumably unstable carbinolamines, there are three pairs of epimeric secondary 1-azabicyclo[3.2.1]-octanols, of which only a 6-ol isomer (*cf.* **4**) of unknown configuration has been previously reported.[2]

The six isomers have been synthesized; their stereochemistry has been assigned. Pertinent physical data are listed in Table I. As expected on the basis of their molecular geometry, none of these isomers shows any infrared absorptions below 2850 cm^{-1} (Bohlmann bands) which are characteristic of two or more C–H bonds being *trans* diaxial to a nitrogen electron pair.[3]

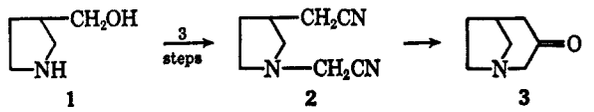
TABLE I

PHYSICAL DATA FOR THE 1-AZABICYCLO[3.2.1]OCTANOLS

Compound	Mp, °C	Glpc retention time, min[a]	pK_a[b]	Nmr, carbinol H τ[c]	Nmr, carbinol H W, cps[d]
3-OH; A (**5**)	175–177	5.0	10.30	6.27	10
3-OH; B (**6**)	132–135	5.4	9.55	6.13	22
4-OH; A (**10**)	180–182	6.4	10.04	6.27	21
4-OH; B (**11**)	184–185	6.7	10.35	6.19	10
6-OH; A (**13**)	177–179	3.7[e]	10.30	5.54	18[f]
6-OH; B (**14**)	157–159	4.0[e]		5.76	12[g]

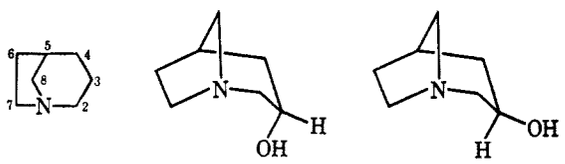
[a] From the air peak on a 10 ft × 1/4 in. column of 13% Carbowax 20M on 60–80 mesh Gas-Chrom P at 230° and a helium flow rate of 110 ml/min. [b] Ionic strength, 0.0050 μ. [c] In 20% $CDCl_3$ solution, from TMS as internal standard. [d] Width of the carbinol proton multiplet at one-half the peak height. [e] From the air peak on a 5 ft × 1/4 in. column of 4% QF-1 on 60–80 mesh Chromosorb W at 135° and a helium flow rate of 55 ml/min. [f] Quintet. [g] Quartet.

1-Azabicyclo[3.2.1]octan-3-ols.—These were obtained from the corresponding ketone **3**, which was synthesized in four steps from the known 3-pyrrolidinemethanol (**1**). Here, the dinitrile **2** was converted by a Thorpe condensation into an iminonitrile, which was not isolated, but was hydrolyzed and decarboxylated directly to the ketone.



1 2 3

The structure of **3**, established by its method of synthesis, is confirmed from the fact that it was hydrogenolyzed to 1-azabicyclo[3.2.1]octane (**4**), the ir spectrum of which was identical with that obtained by hydrogenolysis of the corresponding 4-one and 6-one analogs.[4] Reduction of **3** with lithium aluminum hydride gave a 40:60 mixture of epimeric alcohols, designated A and B according to their order of glpc elution. Hydrogenation of **3** over platinum dioxide gave epimer A (**5**), while reduction with sodium in ethanol–benzene gave epimer B (**6**), each greater than 95% epimerically pure.



4 5 6

The stereochemistry of these alcohols may be assigned by analogy to reductions of the isosteric 3-tropinone system.[5,6] Thus, catalytic hydrogenation would be expected to occur more readily from the less hindered *exo* side of the molecule, giving rise to the axial alcohol (**5**), while a thermodynamically controlled sodium in ethanol reduction should give a predominance of the more stable equatorial hydroxyl isomer (**6**). Relative glpc retention times (Table I) and pK_a values correspond to those previously observed for epimeric axial and equatorial alcohol pairs.[7,8]

These assignments are confirmed by the dilute solution ir spectral data, given in the Experimental Section, which reveal that the axial hydroxyl epimer has a symmetrical free O–H stretching band envelope, of greater extinction coefficient and smaller half band width than that of its equatorial hydroxyl epimer, which has an unsymmetrical band.[9] It may be noted that the O–H stretching maximum occurs at the same

(1) Paper IV: H. S. Aaron, C. P. Rader, and G. E. Wicks, Jr., *J. Org. Chem.*, **31**, 3502 (1966).

(2) L. H. Sternbach and S. Kaiser, *J. Amer. Chem. Soc.*, **74**, 2215 (1952).

(3) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958).

(4) L. P. Reiff and H. S. Aaron, *Tetrahedron Lett.*, 2329 (1967).

(5) L. C. Keagle and W. H. Hartung, *J. Amer. Chem. Soc.*, **68**, 1608 (1946); A. Nickon and L. F. Fieser, *ibid.*, **74**, 5566 (1952).

(6) A. H. Beckett, N. J. Harper, A. D. J. Balon, and T. H. E. Watts, *Tetrahedron*, **6**, 319 (1959).

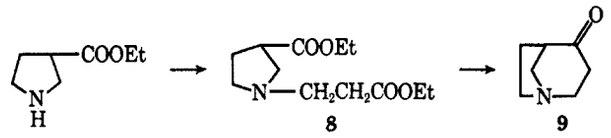
(7) H. S. Aaron, G. E. Wicks, Jr., and C. P. Rader, *J. Org. Chem.*, **29**, 2248 (1964), and references cited therein.

(8) (a) C. P. Rader, R. L. Young, Jr., and H. S. Aaron, *ibid.*, **30**, 1536 (1965); (b) H. S. Aaron and C. P. Rader, *ibid.*, **29**, 3426 (1964).

(9) H. S. Aaron, C. P. Ferguson, and C. P. Rader, *J. Amer. Chem. Soc.*, **89**, 1431 (1967).

frequency in both epimers, in exception to a general rule[9,10] that the axial epimer will absorb at the higher frequency. Nmr spectra showed a half band width of the carbinol proton signal of epimer A to be 10 cps, which suggests an equatorial hydrogen (axial alcohol), while that of epimer B (22 cps) is typical of a strongly coupled axial hydrogen, hence equatorial alcohol.[7,8a] The observation that the equatorial carbinol hydrogen (epimer A) absorbs at higher field than that of its axial epimer is unusual.[11]

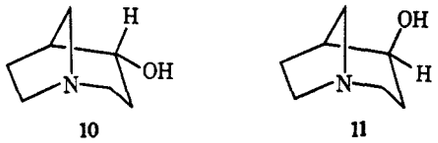
1-Azabicyclo[3.2.1]octan-4-ols.—The parent ketone (**9**) was synthesized[12] by a Dieckmann condensation of **8**, obtained in turn from the known ethyl 3-pyrrolidinecarboxylate (**7**). Compound **9** was reduced



7 **8** **9**

both chemically and catalytically under a variety of conditions to mixtures of epimeric alcohols, as given in the Experimental Section. In every case, epimer A was obtained as the predominant product. The pure epimers were obtained by column chromatography on basic alumina.

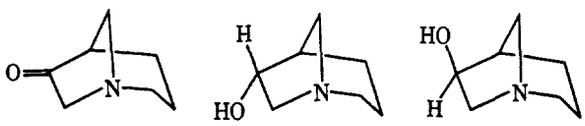
The structure of the ketone **9** was established by its method of synthesis, and by its hydrogenolysis to 1-azabicyclo[3.2.1]octane.[4] The stereochemistry of its derived alcohols may be assigned as **10** (epimer A) and **11** (epimer B) from the reduction data, since for steric reasons, the equatorial alcohol (**10**) would be expected to predominate by either a chemical reduction or a catalytic hydrogenation route. It may be noted



10 **11**

that the relative glpc (Carbowax) retention times (Table I), which are very close for these two epimers, are the reverse of that usually observed for an axial–equatorial alcohol pair. Structures **10** and **11**, however, are confirmed by their pK_a values[8b] and their nmr spectral data (Table I). Both the relative chemical shifts and half band widths of the carbinol protons are in agreement with these assignments.[11,13]

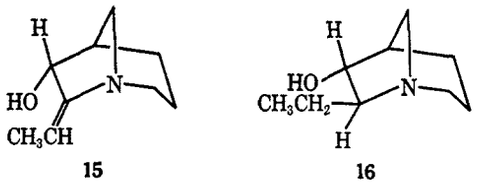
1-Azabicyclo[3.2.1]octan-6-ols.—Catalytic hydrogenation or hydride reduction of 1-azabicyclo[3.2.1]-octan-6-one (**12**) gave the known 6-ol isomer, apparently epimerically pure. The configuration of this alcohol is assigned as *endo* (**13**), based on the assumption that



12 **13** **14**

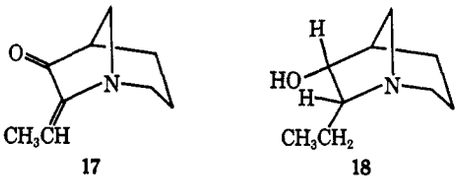
these reductions should all take place from the relatively unhindered *exo* side of the molecule.[14]

Attempts to epimerize the *endo* alcohol with aluminum isopropoxide or sodium ethoxide under equilibrating conditions[6,15] were unsuccessful. The latter reaction, however, led to some interesting and unusual results. Glpc analysis of the product revealed four major components, which were separated by chromatography on alumina. None proved to be the *exo* alcohol **14**. The major component was the *endo* alcohol **13**. Two of the products were assigned from their spectral data and elemental analyses as 7-ethylidene- and 7-ethyl-1-azabicyclo[3.2.1]octan-6-ols (**15** and **16**), respectively. The structure of the fourth component was not established. The relative configurations of **15** and **16** are depicted as deduced below. Compound **15** apparently was obtained as a near equal mixture of *cis* and *trans* isomers, judging from the appearance in the nmr of two (split) methyl peaks of slightly different chemical shift. It appears that **15** and **16** are the products of a



15 **16**

sequence of reactions, which start with an air oxidation of the ethanol solvent to acetaldehyde, followed by an aldol condensation with the ketone **12**, and subsequent dehydration (to **17**) and reduction.



17 **18**

To confirm these structural assignments, the parent ketone **12** was treated with acetaldehyde. The main product was an α,β-unsaturated ketone, **17**, which upon reduction with sodium borohydride gave the identical product (**15**) isolated above. From this mode of synthesis and by analogy to reductions of **12**, compound **15** would be expected to have an *endo*-hydroxyl group. Catalytic hydrogenation of **15** gave a saturated amino alcohol **18**, isomeric with **16**. The stereochemistry of **18** is assigned on the basis that catalytic hydrogenation of **15** should proceed from the less hindered *exo* side of the molecule, while the configuration of the hydroxyl group, of course, would remain unchanged. The configuration of **16**, therefore, is assigned as the C-7 epimer of **18** on the assumption that the configuration at C-6, shown above to be the same in **15** and **18**, should also be the same in **16**,

(10) A. R. H. Cole, P. R. Jefferies, and G. T. A. Müller, *J. Chem. Soc.*, 1222 (1959).

(11) E. L. Eliel, M. H. Gianni, T. H. Williams, and J. B. Stothers, *Tetrahedron Lett.*, 741 (1962).

(12) First synthesized by C. A. Feit and coworkers at Regis Chemical Co., Chicago, Ill., under a U. S. Army Chemical Research and Development Contract. An additional quantity subsequently was prepared in our laboratory from **7**, obtained from Regis. Some of the physical data for **8** and **9** were supplied by Regis.

(13) N. C. Franklin and H. Feltkamp, *Angew. Chem. Intern. Ed. Engl.*, **4**, 774 (1965).

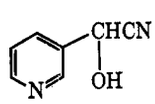
(14) By analogy, the isosteric tropan-6-one molecule is stereospecifically reduced to the 6-α-ol isomer: H. S. Aaron and L. P. Reiff, *J. Heterocycl. Chem.*, **5**, 423 (1968).

(15) M. Balasubramanian and N. Padma, *Tetrahedron*, **19**, 2135 (1963).

since **15** appears to be the precursor of **16** in the reaction from which both were isolated. Further experimentation to establish unequivocally the stereochemistry of these condensation products was not pursued. Based upon these results, the unidentified higher boiling impurities often observed in sodium and alcohol reductions of azabicyclic ketones[1,8a] suggest that side reactions with oxidized solvent may commonly occur under these conditions.

The desired *exo* alcohol (**14**) was finally obtained by a Raney nickel catalyzed epimerization of the *endo* isomer.[16] The configurational assignments of the epimeric alcohols **13** and **14** are supported by the nmr data (Table I), which reveal the carbinol proton signal of **13** to be considerably broader than that of **14**. Inspection of Dreiding models indicates that the orientation of this proton relative to that of the two protons at C-7 is the same in both isomers. Thus, no difference in the band widths of the epimeric carbinol proton signals due to coupling with these protons would be expected. To a first approximation, therefore, the difference in the band widths of the two carbinol proton signals should be due to the difference in coupling constants between them and the C-5 proton. The dihedral angle between the carbinol proton in **13** and the proton at C-5 is about 30°, whereas in **14** this angle is approximately 100°. In general, the magnitude of the coupling constant between vicinal protons is a function of their dihedral angle, being a maximum near 0 and 180°, and a minimum near 90°.[17] It would be expected, therefore, that **13** would have the larger coupling constant between the protons at C-6 and C-5, and thus have the larger carbinol proton band width.

Just prior to the preparation of **14** by the epimerization reaction, above, a synthesis which did not proceed through the ketone **12** was carried out. Here, 3-pyridinecarboxaldehyde cyanohydrin (**19**) was hydrolyzed and esterified to ethyl 3-pyridylglycolate (**20**). The latter was hydrogenated (rhodium on alumina) and reduced (lithium aluminum hydride) to 3-piperidylethylene glycol, which was cyclodehydrated[18] in poor yield to an impure mixture of **13** and **14**, which appeared (ir, after collection by glpc) to be mainly **14**. Optimum conditions for this synthesis were not established, however, in view of the success of the alternate method.



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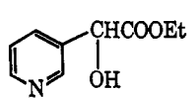

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Experimental Section

The following instrumentation was used, unless otherwise indicated. Nmr analyses were obtained on a Varian A-60 spectrometer, with tetramethylsilane as an internal standard. Ir spectra were obtained on a Perkin-Elmer 237B grating spectrophotometer. Glpc analyses were carried out on a 10 ft × 0.25 in. column of Carbowax 20M, 13% on Gas-Chrom P, at the indicated temperatures and helium flow rates. Reductions and hydrogenations were carried out as previously described.[19] Picrates were prepared in ether and recrystallized from the indicated solvents. Melting and boiling points are uncorrected.

3-Hydroxymethyl-1-pyrrolidineacetonitrile.—3-Pyrrolidinemethanol[20] (**1**), 24 g (0.24 mol), was treated with sodium bisulfite, formaldehyde, and potassium cyanide essentially as described for the synthesis of pyrrolidineacetonitrile,[21] except that the product was extracted with chloroform and dried over potassium carbonate, to give 22 g (66%) of product: bp 105–106° (0.05 mm); ir (neat) 3350 (OH) and 2235 cm^{-1} (weak, CN).

Anal. Calcd for $C_7H_{12}N_2O$: C, 60.0; H, 8.6; N, 20.0. Found: C, 59.6; H, 8.8; N, 19.4.

1,3-Pyrrolidinediacetonitrile (**2**).—An ice-cold solution of 22 g (0.16 mol) of 3-hydroxymethyl-1-pyrrolidineacetonitrile and 45 g of *p*-toluenesulfonyl chloride in 200 ml of pyridine was placed in the refrigerator overnight, then concentrated under reduced pressure at room temperature. The residual oil was dissolved in chloroform, washed with 5% sodium hydroxide solution, then concentrated to give 35 g (77%) of tosylate, a viscous brown oil that could not be induced to crystallize [ir (neat) 2230 (CN) and 1360, 1160 cm^{-1} (SO_2 of tosylate)]. This product was stirred with 23 g of sodium cyanide in 200 ml of dimethyl sulfoxide for 1 hr at room temperature, then 2 hr at 92°, then cooled, diluted with 500 ml of water, and extracted twice with 300 ml of chloroform. The chloroform solution was washed with water and brine, then dried, concentrated, and distilled to give 15 g of **2**, a slightly yellowish oil, bp 120–123° (0.16 mm), which gave a single glpc peak (1.5 min) on a 5-ft column of LAC 446 at 175°. Its ir spectrum showed an intense band at 2245 cm^{-1} (CN) and lacked bands characteristic of the tosylate.

1-Azabicyclo[3.2.1]octan-3-one (**3**).—Compound **2** (14 g, 0.093 mol) was added dropwise over 3 hr to are fluxing slurry (drying tube) of 31 g of potassium *t*-butoxide (MSA Research Corp.) in 700 ml of sodium-dried benzene. The mixture was refluxed for an additional hour, then allowed to stir overnight at room temperature, cooled, and acidified with 10 ml of sulfuric acid in 25 ml of water. After distillation of most of the benzene, the solution was again cooled, and 200 ml of 50 vol % sulfuric acid was added. The remaining benzene was removed as an azeotrope, and the solution was refluxed for 3 hr, then set aside for 48 hr before the work-up was completed. The solution was cooled, brought to pH 12 with 20% sodium hydroxide solution, filtered, and extracted with chloroform. The chloroform solution was dried and concentrated, and the residual brown oil was distilled to give 5.5 g (47%) of **3**, a waxy hygroscopic white solid, which solidified during the distillation, and only an approximate bp 89° (4 mm) was obtained. The product showed a single glpc peak (4.8 min, 210°, 100 ml/min) and melted at 83–87° after two recrystallizations from pentane: ir (neat) 1720 cm^{-1} (C=O). Its picrate was obtained as orange needles from ethanol and orange prisms from ethyl acetate–hexane: mp 197–198° dec.

Anal. Calcd for $C_{13}H_{14}N_4O_8$: C, 44.1; H, 4.0; N, 15.8. Found: C, 44.3; H, 4.2; N, 15.7.

1-Azabicyclo[3.2.1]octan-3-ol, Axial Alcohol, Epimer A (**5**).—An ethanol solution of the ketone **3** was hydrogenated over platinum dioxide for 0.5 hr, filtered, and concentrated under reduced pressure to give **5**, mp 175–177°, which contained (glpc) only a trace, if any, of epimer B. A dilute solution showed these ir data:[9,22] $\nu_{OH}^{CCl_4}$ 3624 cm^{-1}; $\Delta\nu_{1/2}$ 16 cm^{-1}; ϵ 76; α/β 1.0. Its picrate melted at 230–232° dec (isopropyl alcohol).

Anal. Calcd for $C_{13}H_{16}N_4O_8$: C, 43.8; H, 4.5. Found: C, 43.8; H, 4.6.

1-Azabicyclo[3.2.1]octan-3-ol, Equatorial Alcohol, Epimer B (**6**).—A benzene solution of the ketone **3** was reduced with sodium in ethanol as described,[19] except that chloroform was used for the final extraction. The product was obtained as a yellow oil, which contained about 3% epimer A. It was taken up in hot hexane and cooled to give a yellow solid, mp 127–134°, from which pure **6** was collected by preparative glpc as a white solid, mp 132–135°. A dilute solution showed these ir data:[9,22]

(16) E. L. Eliel and S. H. Schroeter, *J. Amer. Chem. Soc.*, **87**, 5031 (1965).

(17) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Inc., New York, N. Y., 1959, p 84.

(18) H. S. Aaron, O. O. Owens, P. D. Rosenstock, S. Leonard, S. Elkin, and J. I. Miller, *J. Org. Chem.*, **30**, 1331 (1965).

(19) C. P. Rader, G. E. Wicks, Jr., R. L. Young, Jr., and H. S. Aaron, *ibid.*, **29**, 2252 (1964).

(20) Y.-H. Wu and R. F. Feldkamp, *ibid.*, **26**, 1519 (1961).

(21) R. H. Reitsma and J. H. Hunter, *J. Amer. Chem. Soc.*, **70**, 4009 (1948).

(22) Recorded by C. P. Ferguson on a Perkin-Elmer 521 grating spectrophotometer.

$\nu_{OH}^{CCl_4}$ 3624 cm^{-1}; $\Delta\nu_{1/2}$ 26.5 cm^{-1}; ϵ 58; α/β 0.64. Its picrate melting point, 198–205°, did not sharpen on recrystallization from acetone–pentane.

Anal. Calcd for $C_{13}H_{16}N_4O_8$: C, 43.8; H, 4.5; N, 15.7. Found: C, 43.8; H, 4.5; N, 15.7.

1-Azabicyclo[3.2.1]octane (4) by Hydrogenolysis of 3.—The ketone **3**, 0.1 g in 5 ml of 0.2 *N* hydrochloric acid, was hydrogenated over 0.05 g of platinum dioxide at 3 atm of hydrogen for 1 hr and worked up in the usual manner.[19] The product (**4**) was obtained as a soft, hygroscopic solid of strong ammoniacal odor, which gave a single glpc peak (0.9 min, 220°, 120 ml/min). Its ir spectrum contained no carbonyl or hydroxyl absorption, and was identical with that obtained by hydrogenolysis of the corresponding 4-one and 6-one analogs. It spicrate melted at 280–284° dec (methanol) (lit.[23] mp 294–295°).

Anal. Calcd for $C_{13}H_{16}N_4O_7$: C, 45.9; H, 4.7; N, 16.5. Found: C, 45.7; H, 4.7; N, 16.6.

A chloroplatinate was prepared, mp 214–216° dec (lit.[23] mp 215–215.5°).

1-Azabicyclo[3.2.1]octan-4-one (9).[12]—Ethyl 3-pyrrolidinecarboxylate (**7**)[20] (18 g, 0.13 mol) and ethyl acrylate (16 g, 0.16 mol) were refluxed for 3 hr in 125 ml of ethanol, then concentrated to give (according to the cognate procedure of Leonard)[24] 30 g (99%) of diethyl pyrrolidine-3-carboxylate-1-β-propionate (**8**). The undistilled product gave a single glpc peak (11.5 min, 237°, 110 ml/min) and was used directly in the next step. An earlier sample, prepared at Regis, had bp 93–97° (0.08 mm), n^{30}D 1.4529.

Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.2; H, 8.7; N, 5.8. Found: C, 59.0; H, 8.8; N, 5.7.

The diester **8** was converted into **9** by the Dieckmann procedure,[24] except potassium isopropoxide in toluene (potassium *t*-butoxide, at Regis) was used for the condensation. The product (**9**), which was difficultly distilled owing to its tendency to solidify in the condenser, gave a single glpc peak (3.6 min, 245°, 120 ml/min) and was obtained as a waxy solid: 9.5 g (61%); mp 84–86°; bp 116° (*ca.* 27 mm); ir ($CHCl_3$, Infracord) 1700 (CO), with a shoulder at 1690 cm^{-1}; picrate mp 233–235°.

Anal. Calcd for $C_{13}H_{14}N_4O_8$: C, 44.1; H, 4.0; N, 15.8. Found: C, 43.9; H, 4.0; N, 15.5.

1-Azabicyclo[3.2.1]octan-4-one Reductions.—Catalytic hydrogenations of the ketone **9** gave the following percentages of epimer A (**10**) in an A/B mixture: ruthenium on carbon in acid, 66%; rhodium on carbon in acid, 76%; platinum dioxide in ethanol, 89%. Palladium on carbon in acid and ruthenium on carbon in ethanol gave little or no reduction, while platinum dioxide in acid gave only the hydrogenolysis product (**4**).[4] Lithium aluminum hydride and sodium in ethanol–benzene reductions gave 74 and 82%, respectively, of epimer A in an A–B mixture.

Epimeric 1-Azabicyclo[3.2.1]octan-4-ols (10 and 11).—A mixture (5.0 g) of the epimeric alcohols, obtained from hydrogenation of **9** over ruthenium on carbon, was dissolved in a little chloroform, then chromatographed on 500 g of neutral alumina (Woelm) which had been packed in chloroform. The progress of the separation was monitored by glpc, and the eluent, containing the indicated product, was collected in the following order: 4 l., chloroform (epimer A); 5 l., chloroform–methanol (9:1) (A and B mixture); and 4 l., methanol (epimer B). In addition, some of the hydrochloride of epimer B was obtained as a chloroform-insoluble brown gum on evaporation of the methanol fraction. Therefore, the column was washed with 2 l. of 5% sodium hydroxide solution, from which an additional quantity of epimer B was eventually recovered. The eluent fractions were evaporated and the respective residues recrystallized from hexane to give epimer A (**10**), 1.4 g of white needles, mp 180–182°, and epimer B (**11**), 0.2 g of white crystals, mp 184–185°. A mixture melting point was undepressed. Picrates (from isopropyl alcohol) melted at 244.5–246° (A) and 220–221° (B), respectively. A mixture of these two picrates melted at 230–235°.

Anal. Calcd for $C_{13}H_{16}N_4O_8$: C, 43.8; H, 4.5. Found for epimer A: C, 43.5; H, 4.3. Found for epimer B: C, 43.9; H, 4.6.

1-Azabicyclo[3.2.1]octan-6-one (12) Reductions. *endo*-1-Azabicyclo[3.2.1]octan-6-ol (13).—The ketone **12** was prepared[25] as described.[2] Hydrogenation over palladium on carbon in aqueous acid or ethanol or ruthenium on carbon in aqueous acid gave little or no reduction, while use of platinum dioxide produced considerable hydrogenolysis product (**4**), isolated by preparative glpc and identified by ir analysis.[4] Reduction with lithium aluminum hydride, or hydrogenations over platinum dioxide in ethanol, or rhodium on carbon in ethanol or 0.2 *N* hydrochloric acid gave the *endo* alcohol **13**, mp 177–179° (cyclohexane) (lit.[2] mp 177–179°), apparently epimerically pure, as judged from the identity of these ir spectra. The picrate melted at 224–225.5° (lit.[2] mp 224–226°). A tosylate, mp 107–109° (hexane), was prepared by the Schotten–Baumann procedure at 10°.[26]

Anal. Calcd for $C_{14}H_{19}NO_3S$: C, 59.8; H, 6.8; S, 11.4. Found: C, 59.6; H, 6.8; S, 11.4.

***exo*-1-Azabicyclo[3.2.1]octan-6-ol (14).**—An aqueous slurry of sponge nickel catalyst (Davison Chemical Co.) was washed by decantation with distilled water until neutral, then three times each with ethanol and benzene. The residual alcohol was distilled as an azeotrope from the benzene suspension of the catalyst, and 1 g of the resultant slurry was added to 0.5 g of the *endo* epimer (**13**) in 40 ml of benzene, then refluxed (drying tube) for 24 hr, filtered, and concentrated. Glpc analysis revealed the product to consist of a 60:40 mixture of the ketone **12** and what proved to be the *exo* alcohol (**14**). The epimeric alcohols have identical retention times on Carbowax, but partially separated on QF-1. A third of this solution was chromatographed on 12 g of basic alumina (Woelm, grade IV) using successively hexane, ether, and methanol for elution. The ketone was obtained from the ether fraction. The methanol fraction was concentrated, and the residue was crystallized from cyclohexane to give 26 mg of the *exo* alcohol (**14**), mp 157–159°, mass spectrum mol wt 127.137 amu (theory 127.140 amu). Its ir spectrum differed from that of the *endo* epimer, most notably by the absence of a strong band at 1100 cm^{-1} and the appearance of a new band at 1040 cm^{-1} (probably C–O). A picrate was obtained as small orange prisms, mp 240–241.5° (from ethyl acetate–cyclohexane), mmp 213–223° (with **13** picrate).

Reduction of 1-Azabicyclo[3.2.1]octan-6-one (12) with Sodium in Ethanol. Attempted Epimerization of 13.—The ketone **12** (5. g, 0.04 mol) in 80 ml of ethanol was added dropwise over 1 hr with stirring to 10 g of freshly cut sodium in 80 ml of sodium-dried benzene, then refluxed for 1 hr with stirring. The remaining sodium was then destroyed by the addition of 40 ml of ethanol. Additional ketone (0.5 g) was added, and the solution was refluxed for 16 hr. Water (100 ml) was added, and the aqueous phase was extracted with five 100-ml portions of chloroform. The combined organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to give 4.9 g of a viscous brown oil, which was found (glpc) to contain four major components, designated B (smallest), C (largest), D, and E, in order of increasing retention time. (A small amount of a product, observed as component A in an earlier small scale run, was not observed in this experiment.) When the product mixture was triturated with hot benzene–cyclohexane, the major portion dissolved and left a solid residue (1.0 g), which appeared to be mainly the hydrochloride of **13**. The solution was concentrated under reduced pressure to 3.0 g of a brown oil, which was chromatographed on 250 g of basic alumina (Woelm, IV), prepared in benzene, and eluted with ether (1300 ml) and methanol (800 ml), respectively. The eluent was collected in 100-ml fractions, concentrated, and analyzed by glpc. The order of elution from the column was A, (position determined from the previous run), D, B, E, and C. Although most of the fractions consisted of mixtures, each component was obtained essentially pure by evaporation of selected fractions. Component C was found (glpc, ir, melting point, and picrate) to be identical with the *endo* alcohol **13**, obtained by hydrogenations of **12** above. Component D was recrystallized from cyclohexane to give 7-ethylidene-1-azabicyclo[3.2.1]octan-6-ol (assigned *endo*), **15**: mp 91.5–93°; mass spectrum mol wt 153 (theory 153); ir (CCl_4) 3627 (O—H), 3012 (weak, vinylic C—H), 1688 (HC=C, *exo* to a five-membered ring), 1450 (CH_2 and CH_3), and 1380 cm^{-1} (CH_3); nmr (20% $CDCl_3$) τ 8.28 and 8.31 (two d of near equal intensity, 3, J = 7 cps for each, C=CH—CH_3,

(23) V. Prelog, S. Heimbach, and E. Cerkonikov, *J. Chem. Soc.*, 677 (1939).

(24) N. J. Leonard, S. Swann, and J. Figueras, *J. Amer. Chem. Soc.*, **74**, 4620 (1952).

(25) Synthesized by Dr. A. Y. Garner and coworkers, Monsanto Research Corp., Dayton, Ohio, from intermediates supplied by Mr. F. F. Frulla and coworkers, Olin–Mathieson Chemical Corp., New Haven, Conn., under U. S. Army Research and Development Contracts.

(26) A. I. Vogel, "Practical Organic Chemistry," 3rd ed, John Wiley & Sons, Inc., New York, N. Y., 1956, p 784.

cis/trans), 8.1 (m, 5, CH_2 and CH not adjacent to N), 7.0 (m, 4, CH_2 adjacent to N), 5.68 (s, 1, OH), 5.28 (m, 1, CH—OH), and 4.73 (q, 1, J = 7 cps, C=CH—CH_3). A picrate was obtained as bright yellow needles, mp 172.5–175° (from ethyl acetate–benzene).

Anal. Calcd for $C_{15}H_{18}N_4O_8$: C, 47.1; H, 4.8; O, 33.5. Found: C, 47.0; H, 4.9; O, 33.4.

Component E was recrystallized from hexane to give 0.09 g of needles, assigned as 7-(*exo*)ethyl-1-azabicyclo[3.2.1]octan-6-(*endo*)ol (**16**): mp 95–96°; ir (CCl_4) 3628 (O—H), 1465 (CH_3 and CH_2), and 1385 cm^{-1} (CH_3). A picrate was obtained as iridescent yellow needles, mp 192–194° (from ethyl acetate–benzene).

Anal. Calcd for $C_{15}H_{20}N_4O_8$: C, 46.9; H, 5.3; O, 33.3. Found: C, 47.0; H, 5.2; O, 33.6.

Component B was purified by sublimation (60–75°, 0.015 mm) to give 5 mg of a waxy solid, mp 100–132°, which showed OH, CH_2, and CH_3 bands in the ir spectrum. However, insufficient material was available for further purification and characterization.

Hydrogenation of 7-Ethylidene-1-azabicyclo[3.2.1]octan-6-ol (15).—Component D (**15**), 0.10 g in 5 ml of ethanol, was hydrogenated over 0.05 g of platinum dioxide at 40 psig for 0.5 hr, filtered, and concentrated to give 0.09 g of an oil which solidified on standing overnight. The oily crystals were triturated under hexane to give a product assigned as 7-*endo*-ethyl-1-azabicyclo-[3.2.1]octan-6-*endo*-ol (**18**): mp 85–90°; ir (CCl_4) 3630 cm^{-1} (OH), no olefinic stretching absorption. The compound gave a single glpc peak of identical retention time with **16**. However, their ir spectra differed in the fingerprint region. Its picrate melted at 213.5–215°.

Anal. Calcd for $C_{15}H_{20}N_4O_8$: C, 46.9; H, 5.3; O, 33.3. Found: C, 46.6; H, 5.2; O, 33.1.

7-Ethylidene-1-azabicyclo[3.2.1]octan-6-one (17).—Compound **12** (0.5 g, 0.004 mol) with 0.35 g (0.008 mol) of acetaldehyde was kept in a pressure bottle in a 53° oven for 7 days and at room temperature for 21 days, then concentrated under reduced pressure. Glpc analysis (227°, 43 ml/min) revealed a small amount of **12**, three minor unidentified components (possibly acetaldehyde selfcondensation products), and a major component of longer retention time, **17**, whose ir (neat, sample collected by glpc) spectrum showed strong bands at 1732 (C=O) and 1660 cm^{-1} (conjugated C=C). Attempts to crystallize the product were not successful, even after chromatography over basic alumina with ether. A picrate was obtained as yellow plates, mp 160–161° (from ethyl acetate–benzene).

Anal. Calcd for $C_{15}H_{16}N_4O_8$: C, 47.4; H, 4.2; O, 33.7. Found: C, 47.7; H, 4.2; O, 33.4.

7-Ethylidene-1-azabicyclo[3.2.1]octan-6-ol (15).—Crude **17**, 0.40 g (0.0025 mol), was added to 0.10 g (0.0026 mol) of sodium borohydride in 5 ml of water plus 1 drop of 20% sodium hydroxide solution, then placed on the steam bath for 0.5 hr. Concentrated ammonium hydroxide solution (1 ml) was added, and the product was extracted with chloroform, which was dried ($MgSO_4$) and concentrated. Glpc analysis revealed a single volatile component, mp 85–91° (as collected from the column), whose ir spectrum was identical with that of **15**, obtained above as component D.

3-Pyridinecarboxaldehyde Cyanohydrin (19).—3-Pyridinecarboxaldehyde (Aldrich Chemical Co.), 22 g (0.21 mol), was treated with hydrochloric acid and aqueous potassium cyanide as described for the 5-methyl analog.[27] The product was filtered and used as the moist precipitate in the next step. In another run, a 92% yield of **19**, mp 38–52°, was obtained as unstable white crystals, which yellowed on standing and had the odor of hydrogen cyanide.

Ethyl 3-Pyridylglycolate (20).—The crude **19** was refluxed with 100 ml of concentrated hydrochloric acid for 18 hr, then concentrated, and finally dried on the steam bath under reduced pressure for 1 hr. The salt mixture thus obtained (37 g) was refluxed (drying tube) with 125 ml of ethanol and 2.5 ml of sulfuric acid for 18 hr, concentrated, cooled, and made basic with saturated sodium carbonate solution. The product was extracted with chloroform, dried ($MgSO_4$), concentrated, and distilled to give 19 g (50% over-all) of **20**: bp 86° (0.05 mm); $n^{25}D$ 1.5156. Its picrate was obtained as yellow needles, mp 103–104° (methanol).

Anal. Calcd for $C_{15}H_{14}N_4O_{10}$: C, 43.9; H, 3.4; O, 39.0. Found: C, 43.8; H, 3.2; O, 38.5.

Registry No.—3-Hydroxymethyl-1-pyrrolidineacetonitrile, 17604-26-1; **2**, 17604-27-2; **3**, 17604-28-3; **3** picrate, 17604-29-4; **4**, 279-92-5; **5**, 17628-91-0; **5** picrate, 17629-14-0; **6**, 17628-92-1; **6** picrate, 17629-15-1; **8**, 17604-85-2; **9**, 17604-77-2; **9** picrate, 17604-78-3; **10**, 17629-13-9; **10** picrate, 17628-84-1; **11**, 17628-85-2; **11** picrate, 17628-93-2; **13**, 17628-86-3; **14**, 17628-87-4; **14** picrate, 17628-88-5; **15**, 17628-89-6; **15** picrate, 17628-90-9; **16**, 17603-93-9; **17**, 17604-71-6; **17** picrate, 17604-72-7; **18**, 17604-73-8; **19**, 17604-74-9; **20**, 17604-75-0; **16** picrate, 17603-94-0; **18** picrate, 17603-95-1; **20** picrate, 17604-76-1.

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