[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, URBANA, ILL.]

Unsaturated Amines. XVI. An Oxidative Cyclization Route to Oxazolidines and Tetrahydro-1,3-oxazines[1,2]

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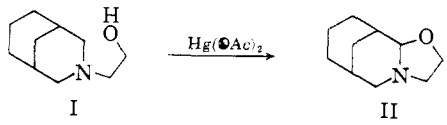
The mercuric acetate oxidation of many piperidino- and pyrrolidino-alcohols can be controlled to give fair to good yields of bicyclic oxazolidines and tetrahydro-1,3-oxazines where the masked aldehyde or ketone carbon atom is at the bridgehead. Representative bicyclic systems have been obtained for the first time by this method. The main side reaction is over-oxidation to give amidoalcohols, and the oxidation may also be used as a route to these compounds as major products. The stereochemistry of many of the bicyclic oxazolidines and tetrahydro-1,3-oxazines can be assigned tentatively by observing the infrared bands in the 2700–2800 cm.$^{-1}$ region and by applying conformational analysis.

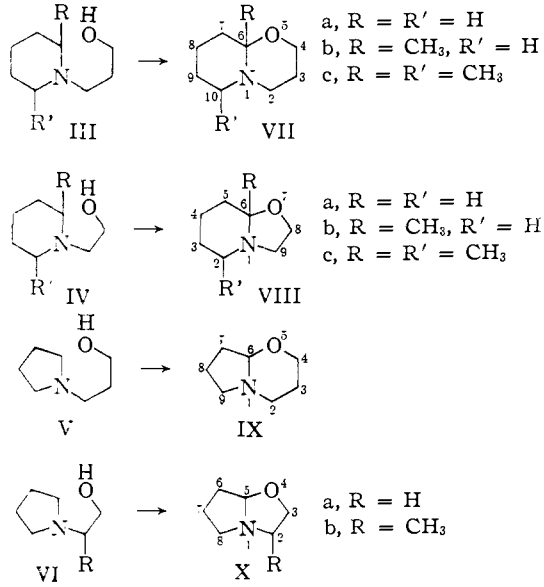
We provided earlier a single example of oxazolidine ring formation by the mercuric acetate oxidation of a β-3°-aminoalcohol.[4] Further experiments have now shown that the new ring closure method is generally applicable to the synthesis of oxazolidines and tetrahydro-1,-3-oxazines.[5] Since the mercuric acetate oxidation had previously been tried only with a bicyclic aminoalcohol, 3-hydroxyethyl-3-azabicyclo[3.3.1]nonane (I) (→ 3-oxa-6-azatricyclo[6.3.1.$0^{2,6}$]dodecane[6] (II)), in



I II

which enamine formation within the ring system was impossible, the use of an aminoalcohol that did not possess a bridgehead β_N-carbon was a possible invitation to enamine alcohol formation followed by dimerization to complex products. It is possible to distinguish between the original tertiary aminoalcohol, the corresponding enamine alcohol and the oxazolidine or tetrahydro-1,3-oxazine by infrared spectroscopy and vapor phase chromatography.[7] The infrared spectra of the enamine alcohols show absorption maxima in the 1650 and 3400 cm.$^{-1}$ regions, while the spectra of the oxazolidines or tetrahydro-1,3-oxazines are transparent in these regions but should possess at least three strong bands in the 1000–1200 cm.$^{-1}$ region, characteristic of the N–C–O grouping.[8,9] The bicyclic oxazolidines prepared earlier by Conrow and Sauers[4,7] formed picrate derivatives which were shown to be in the open, iminium salt form by their infrared spectra ($>C{=}\overset{+}{N}<$ absorption at *ca.* 1675 cm.$^{-1}$ and O–H absorption at 3300 cm.$^{-1}$) so that such a derivative may not necessarily permit a decision as to whether the basic precursor is an oxazolidine or an enamine alcohol.

The tertiary aminoalcohols studied were 3-piperidinopropanols (III), 2-piperidinoethanols (IV), 3-pyrrolidinopropanols (V) and 2-pyrrolidinoethanols (VI). These starting materials are listed in Table I (see Experimental). Since the mercuric acetate attack on substituted 1-methylpiperidines proceeded to give oxidation products in better yields[10] than the oxidation of substituted 1-methylpyrrolidines,[11] we decided to study the alkylated piperidinoalcohols in greater detail than the pyrrolidinoalcohols.[12–14]



(1) Presented at the 136th Meeting of the American Chemical Society, Atlantic City, N. J., September 13–18, 1959; see Abstracts of Papers, p. 25-P.

(2) For article XV in this series, see N. J. Leonard and W. K. Musker, THIS JOURNAL, **81**, 5631 (1959).

(3) USI (U. S. Industrial Chemicals Co.) Fellow, 1958–1959.

(4) N. J. Leonard, K. Conrow and R. R. Sauers, THIS JOURNAL, **80**, 5185 (1958).

(5) Other reagents which provide isolated examples of N–C–O ring formation, in the alkaloid series, are osmium tetroxide in ether (M. F. Bartlett, J. Edwards, W. I. Taylor and K. Wiesner, *Chemistry & Industry*, 323 (1953); S. W. Pelletier and W. A. Jacobs, THIS JOURNAL, **78**, 4144 (1956)); silver oxide in methanol (K. Wiesner, Z. Valenta, J. F. King, R. K. Maudgal, L. G. Humber and Shô Itô, *Chemistry & Industry*, 173 (1957)); potassium permanganate (F. Sparatore, R. Greenhalgh and L. Marion, *Tetrahedron*, **4**, 157 (1958)); and potassium ferricyanide (S. Sakai, *Chem. and Pharm. Bull.*, **6**, 448 (1958)).

(6) This compound is now named in the 3-oxa-6-aza-sequence rather than the 6-aza-3-oxa-sequence to conform with *Chemical Abstracts* usage.

(7) The index of refraction can be employed as a guide to indicate the presence of large amounts of enamine since it has been found that the value for the enamine alcohol is usually 0.02 unit higher than that for either the oxazolidine or the aminoalcohol (R. R. Sauers, Ph.D. Thesis, University of Illinois, 1957).

(8) E. D. Bergmann, E. Zimkin and S. Pinchas, *Rec. trav. chim.*, **71**, 168 (1952), and the eight articles following.

(9) E. D. Bergmann, D. Lavie and S. Pinchas, THIS JOURNAL, **73**, 5662 (1951).

(10) N. J. Leonard and F. P. Hauck, Jr., *ibid.*, **79**, 5279 (1957).

(11) N. J. Leonard and A. G. Cook, *ibid.*, **81**, 5627 (1959).

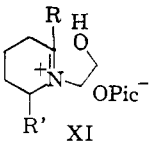
(12) R. O. Clinton, U. J. Salvador and S. C. Laskowski, *ibid.*, **71**, 3366 (1949).

(13) D. E. Adelson, L. G. MacDowell and C. B. Pollard, *ibid.*, **57**, 1988 (1935).

(14) F. H. Buckwalter and A. P. Granatek, U. S. Patent 2,682,539, June 29, 1954; *C. A.*, **49**, 9042 (1955).

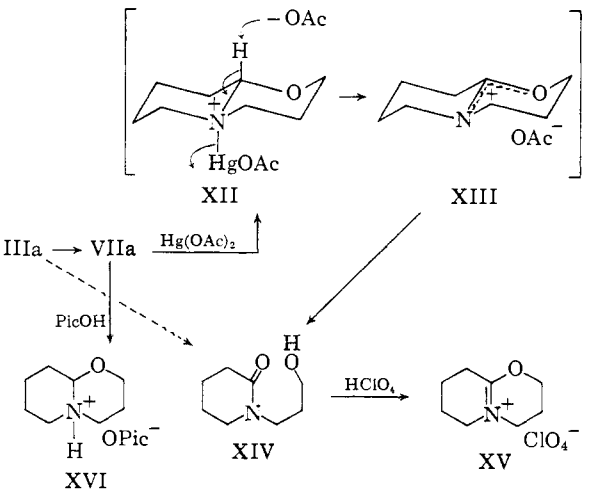
Mercuric Acetate Oxidation of *tert.*-Aminoalcohols.—The mercuric acetate oxidation of many piperidino- and pyrrolidino-alcohols (III-VI) can be controlled to give fair to good yields of bicyclic oxazolidines and tetrahydro-1,3-oxazines where the masked aldehyde or ketone carbon atom is at the bridgehead. The bicyclic systems which have been obtained by this method are illustrated by formulas VII-X, and details as to yields and physical properties are provided in Table II (see Experimental). The general system which we have used in naming these compounds may be illustrated by two examples: 6,10-dimethyl-5-oxa-1-azabicyclo[4.4.0]-decane for VIIc and 2,6 - dimethyl - 7 - oxa - 1-azabicyclo[4.3.0]nonane for VIIIc. The oxidation was carried out at room temperature whenever possible. When the rate of oxidation was very slow, as indicated by the rate of precipitation of mercurous acetate, the reaction was usually warmed so that the theoretical amount of mercurous acetate (calculated for a two-electron oxidation) would be precipitated within a convenient time. The mercurous acetate was removed by filtration, the excess mercuric ion by conversion to the insoluble sulfide and filtration. The sequence of basification with potassium carbonate, ether extraction, solvent removal and fractional distillation of the residue was used for isolation of the products.

The mercuric acetate oxidation of piperidinoethanols was generally found to produce bicyclic oxazolidines in conversions of 47 to 75%. The course of the reaction is regarded as an internal nucleophilic attack by the alcohol group on the ternary iminium salt formed in the initial oxidation stage.[4] The contaminating enamine alcohols and starting materials were eliminated by distillation. The formation of small amounts of amidoalcohol and amidoester were noted in the high-boiling fractions obtained from the oxidation of 2-piperidinoethanol (IVa) and 2-(3′-methylpiperidino)-ethanol under mild conditions. No high-boiling fraction was isolated from the oxidation of 2-(2′,6′-dimethyl-piperidino)-ethanol (IVc). When substituents were present on the 2- or 6-position of the piperidine ring, the yield of bicyclic oxazolidine was increased. We have assigned the structure of the oxazolidine resulting from the oxidation of 2-(2′-methylpiperidino)-ethanol (IVb) as 6-methyl-7-oxa-1-azabicyclo[4.3.0]nonane (VIIIb) by analogy with the oxidation of 1,2-dimethylpiperidine by mercuric acetate,[10] which yielded 1,2-dimethyl-Δ^2-tetrahydropyridine, corresponding to preponderant oxidation on the tertiary α_N-carbon. In the oxidation product of 2-(2′-methylpiperidino)-ethanol a very weak shoulder was noted on the main oxazolidine peak by vapor phase chromatography, which may be due to a small amount of 2-methyl-7-oxa-1-azabicyclo[4.3.0]nonane. When the oxidation of IVb was carried out at high temperature for a long period of time, a very small amount (1%) of the mixed amides was obtained. This product indicated that some dehydrogenation had occurred at the 6-position, since it is unlikely that the oxazolidine formed by cyclization to the 2-position could be oxidized to an amidoalcohol. Consistent with earlier findings, the picrates formed from 6-methyl-7-oxa-1-azabicyclo[4.3.0]nonane (VIIIb) and 2,6-dimethyl-7-oxa-1-azabicyclo[4.3.0]-nonane (VIIIc) were in the open, iminium salt form (XI), as determined by infrared.



XI

As in the case of the 2-piperidinoethanols, compounds with substituents in the 2′-or 6′-position in the piperidine ring of 3-piperidinopropanols (III) gave better yields of bicyclic tetrahydro-1,3-oxazines (VII) than did the unsubstituted aminoalcohol. Yields of the cyclic products from the 3-piperidinopropanols were generally lower than from the corresponding 2-piperidinoethanols. For example, the maximum conversion from 3-piperidinopropanol (IIIa) to 5-oxa-1-azabicyclo[4.4.0]-decane (VIIa) was 36%. 2-Methyl- and 2,6-dimethylpiperidinopropanols (IIIb, c) gave bicyclic tetrahydro-1,3-oxazines (VIIb, c) in 65% conversions. Over-oxidation generally yielded amidoalcohols. 1-(3′-Hydroxypropyl)-2-piperidone (XIV) was formed in 20% yield using mild oxidation conditions with IIIa; however, when the oxidation was performed for a longer time, the amidoalcohol was isolated in 50% yield. The identity of the amidoalcohol was confirmed by comparing its properties with the known compound prepared by Middleton[15] by reducing the corresponding pyridone with Raney nickel. Moreover, the compound formed by the addition of perchloric acid to the amidoalcohol was identical with 2,3-tetramethylene-5,6-dihydro-1,3,4-oxazinium perchlorate (XV).[15] In order to show that the amidoalcohol could be formed from the tetrahydro-1,3-oxazine or its equivalent in the acid-buffered solution, we subjected 5-oxa-1-azabicyclo[4.4.0]-decane (VIIa) to mercuric acetate oxidation and did indeed obtain 1-(3′-hydroxypropyl)-2-piperidone (XIV). The possibility that the tetrahydro-1,3-oxazine is one precursor in the mildly acidic

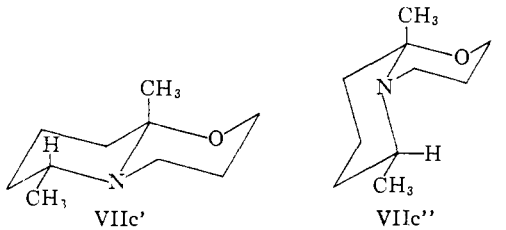


(15) W. J. Middleton, University of Illinois, unpublished results, 1952.

solution, through the oxidation stage XII and the hydrolysis stage XIII, is attractive since a salt such as the picrate of VIIa, for example, is in the closed form (XVI). However, hydroxy (III, R = OH, R′ = H) and acetoxy (III, R = OAc, R′ = H) forms are also possible precursors.

Weak broad enamine absorption in the 1650 cm.$^{-1}$ region of the infrared spectrum can not easily be distinguished from lactam absorption (*ca.* 1610–1645 cm.$^{-1}$ [16,17]). However, we observed that both five- and six-membered tertiary lactams give rise to a companion band at 1490–1505 cm.$^{-1}$.[18] This band is usually strong and sharp in contrast to the broad lactam absorption at higher frequency. In addition, the pure amidoalcohol displays an O–H stretching vibration at 3400 cm.$^{-1}$ which is usually sharper than the O–H absorption in the tertiary aminoalcohol and the enamine alcohol.

The oxidation of 3-(2′-methylpiperidino)-propanol (IIIb) with mercuric acetate yielded a mixture of two bicyclic tetrahydro-1,3-oxazines, 6-methyl-5-oxa-1-azabicyclo[4.4.0]decane (VIIb) and 10-methyl-5-oxa-1-azabicyclo[4.4.0]decane (VII, R = H, R′ = CH_3), with the former predominating by a factor of approximately nine according to vapor phase chromatography. When the reaction was performed using a higher temperature and a longer time, the ratio of isomers was about the same and a trace of amidoalcohol was detected. This is approximately the same result experienced with 2-(2′-methylpiperidino)-ethanol (IVb) except that the yield of the isomeric product is much greater from the piperidinopropanol than from the piperidinoethanol. The oxidation of 3-(2′,6′-dimethylpiperidino)-propanol (IIIc) gave 6,10-dimethyl-5-oxa-1-azabicyclo[4.4.0]decane (VIIc). When the sample was subjected to vapor phase chromatography a shoulder on the main peak was observed. This shoulder may indicate that both stereoisomers (*dl*-pairs) of 6,10-dimethyl-5-oxa-1-azabicyclo[4.4.0]decane are produced (VIIc′ and VIIc″, representing racemates).



The oxidation of 3-(3′,5′-dimethylpiperidino)-propanol (XVII) with mercuric acetate yielded solely the amidoalcohol, 1-(3′-hydroxypropyl)-3,5-dimethyl-2-piperidone (XVIII). No trace of bicyclic tetrahydro-1,3-oxazine was found. Moreover, the amido-alcohol XVIII did not undergo cyclization to a dihydroöxazinium perchlorate, in contrast to the compound lacking the methyl groups (XIV → XV).

Two β-pyrrolidinoalcohols were used in this study, 2-pyrrolidinopropanol (VIb) and 2-pyrrolidinoethanol (VIa). Both gave lower conversions (25% range) to bicyclic oxazolidines (Xb, a) on mercuric acetate oxidation than did the piperidinoethanols. The oxidation of 3-pyrrolidinopropanol (V) to 5-oxa-1-azabicyclo[4.3.0]nonane (IX) proceeded very slowly at room temperature so that the oxidation was performed at steam-bath temperature for 4 hours. The structure of the bicyclic system was checked by reducing the bicyclic tetrahydro-1,3-oxazine with lithium aluminum hydride to the original starting material, which was isolated as the benzoate hydrochloride in 90% yield.

Picrates of most of the bicyclic oxazolidines and tetrahydro-1,3-oxazines were obtained. 7-Oxa-1-azabicyclo[4.3.0]nonane (VIIIa) was exceptional in not forming a stable picrate. It was shown by infrared evidence that the picrates of the bicyclic oxazolidines VIIIb and c. along with that of 6,10-dimethyl-5-oxa-1-azabicyclo[4.4.0]decane (VIIc), existed in the open, iminium salt form ($>C{=}N^{+}<$ absorption 1660–1675 cm.$^{-1}$, O–H absorption 3340 cm.$^{-1}$). The other picrates which were prepared showed no $>C{=}\overset{+}{N}<$ or O–H absorption and therefore exist in the bicyclic form ($>\overset{+}{N}—H$ absorption in the 2600–2800 cm.$^{-1}$ region). If the picrate formation is equilibrium controlled, whether a closed-ring or open-ring picrate is isolated may depend on the relative stabilities of the carbocyclic-type system (XVI being analogous with *trans*-decalin) representing the closed form and of the $>\overset{+}{C}{=}N<$ group in the open form, or, in the extreme, on the relative solubilities of the possible picrate forms.

Stereochemical Considerations.—Since the bridgehead nitrogen atom in the free bases is capable of inversion, the *trans* and *cis*-ring fusions of unsubstituted quinolizidine and octahydropyrrocoline and of 5-oxa-1-azabicyclo[4.4.0]decane (VIIa′ and VIIa″) and of 7-oxa-1-azabicyclo-[4.3.0]nonane (VIIIa′ and VIIIa″) (all as racemates) are interconvertible. The number or degree of nonbonded interactions for the *trans* forms, VIIa′ and VIIIa′, is smaller than that for the *cis* fused rings, in analogy with *trans*-decalin and *trans*-hydrindan,[19–22] and hence the *trans* forms are regarded as the favored conformations (of VIIa and VIIIa). Infrared absorption in the

(16) G. Stork and R. K. Hill, THIS JOURNAL, **79**, 495 (1957).

(17) E. E. van Tamelen, M. Shamma and P. Aldrich, *ibid.*, **78**, 4628 (1956).

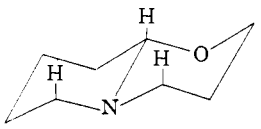
(18) H. M. Randall, R. G. Fowler, N. Fuson and J. R. Dangl, "Infrared Determination of Organic Structures," D. Van Nostrand Company, Inc., N. Y., 1949.

(19) W. G. Dauben and K. S. Pitzer in "Steric Effects in Organic Chemistry," M. S. Newman, ed., John Wiley and Sons, Inc., New York, N. Y., 1956.

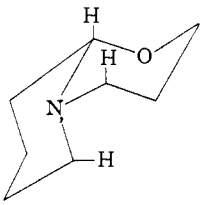
(20) N. L. Allinger, *J. Org. Chem.*, **21**, 915 (1956).

(21) D. H. R. Barton and R. C. Cookson, *Quart. Revs.*, 10, 44 (1956).

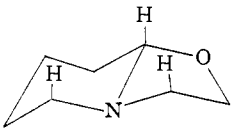
(22) G. Quinkert, *Experientia*, **13**, 381 (1957).



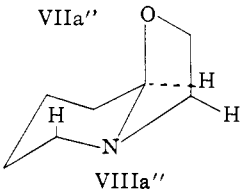
VIIa'



VIIa''



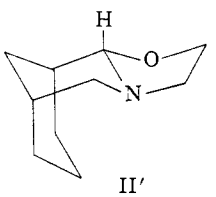
VIIIa'



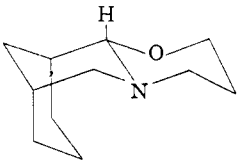
VIIIa''

2700–2800 cm.$^{-1}$ region (general region, not exact limits) may be used to support the presence of the *trans* conformations by application of the empirical relations which Bohlmann found to hold in the quinolizidine series, namely, that when at least two α-hydrogen atoms are *trans* coplanar to the electron pair on the bridgehead nitrogen atom, a pair of bands appears in this region.[23] Specifically, he found that when a *trans* fused quinolizidine ring was present, there were two absorption bands in the 2700–2800 cm.$^{-1}$ region, but when a *cis* fused quinolizidine ring was present, the doublet was not observed.[24-25] Two maxima were observed in the 2700–2800 cm.$^{-1}$ region for 5-oxa-1-azabicyclo[4.4.0]decane in carbon tetrachloride.[26] The *trans* ring geometry is favorable for explaining the further oxidation of 5-oxa-1-azabicyclo[4.4.0]decane with mercuric acetate in aqueous acetic acid (XII→XIII→XIV); *trans* coplanarity of the hydrogen on the α-carbon with the N–Hg bond in the mercurated complex has been shown to be an important steric condition for oxidation in the bicyclic tertiary amine series.[27] The infrared spectrum (CCl_4) of 7-oxa-1-azabicyclo[4.3.0]nonane also exhibited bands in the 2700–2800 cm.$^{-1}$ region, consistent with the presence or predominance of the trans conformation VIIIa'.

The *trans* configuration II' of the oxazolidine moiety in 3-oxa-6-azatricyclo[6.3.1.$0^{2,6}$]dodecane is consistent with the infrared bands in the 2700–2800 cm.$^{-1}$ region (liquid film) and is now favored[4] on the basis of probable equilibrium-controlled ring closure which should lead to the product having the lower magnitude of non-bonded interactions.[20,28] The ring homolog, 3-oxa-7-azatricyclo[7.3.1.$0^{2,7}$]-tridecane, exhibits infrared maxima at 2740,

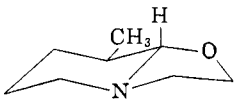


II'

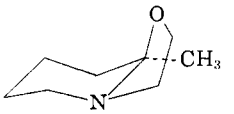


XIX

2790 (~) and 2840 cm.$^{-1}$ and thus may be described by the more stable *trans* configuration XIX.[29] The geometry favored for 5-methyl-7-oxa-1-azabicyclo[4.3.0]nonane,[30] which was synthesized by the sodium and butanol reduction of 1-hydroxyethyl-3-methyl-2-pyridone, on the basis of the 2700–2800 cm.$^{-1}$ region infrared maxima (liquid film), is illustrated by XX. By contrast, the isomeric 6-methyl-7-oxa-1-azabicyclo[4.3.0]-nonane (VIIIb), from IVb, showed no bands in this region (CCl_4). A preference for the *cis* conformation (VIIIb') would here be consistent with the lower energy form of 8-methylhydrindan.[20]

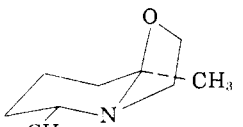


XX

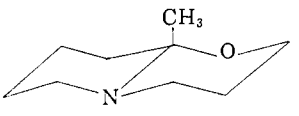


VIIIb'

No bands were found in the 2700–2800 cm.$^{-1}$ region of the infrared spectrum of the bicyclic product resulting from the oxidation of 2-(2',6'-dimethylpiperidino)-ethanol (IVc), and since the non-bonded interaction will be less in the *cis*-fused ring system with the 2-methyl group in an equatorial position, we have tentatively assigned the



VIIIc'



VIIb'

stereochemistry represented by VIIIc' (*dl* pair) to 2,6-dimethyl-7-oxa-1-azabicyclo[4.3.0]nonane. The *trans* conformation of 6-methyl-5-oxa-1-azabicyclo[4.4.0]decane (VIIb'), similar to *trans*-9-methyldecalin, is preferred (maxima in the 2700–2800 cm.$^{-1}$ region), but contributions of the conformation having *cis* ring fusion would not be detected by the infrared method.

The spectrum of 5-oxa-1-azabicyclo[4.3.0]nonane (IX) showed a very weak band of 2710 cm.$^{-1}$ and a strong band at 2840 cm.$^{-1}$ and in general lower intensity absorption in this region than exhibited by the isomeric 7-oxa-1-azabicyclo[4.3.0]nonane (VIIIa) under the same conditions. The bicyclo-[3.3.0]octane systems having *cis*-fused rings comparable to pyrrolizidine derivatives. The infrared spectra of 4-oxa-1-azabicyclo[3.3.0]octane (Xa) and 2-methyl-4-oxa-1-azabicyclo[3.3.0]octane (Xb) showed no absorption in the 2700–2800 cm.$^{-1}$ region and amide formation by overoxidation was negligible. It is of interest to note that pyrrolizidine[23] is not oxidized under the normal mercuric acetate conditions.

(23) F. Bohlmann, Ber., **91**, 2157 (1958). The appearance of these bands is actually more general: well-defined bands in the 2700–2800 cm.$^{-1}$ region are observed for many cyclic and acyclic alkyl tert-amines (W. B. Wright, Jr., *J. Org. Chem.*, **24**, 1362 (1959); G. F. Smith and J. T. Wróbel, *J. Chem. Soc.*, 1463 (1960); Prof. C. A. Grob, University of Basel, personal communication). However, in the examples presently accumulated the pair of strong maxima is *not* present when HC—N—CH conformations of the type specified by Bohlmann | *cannot* exist.

(24) F. Bohlmann and C. Arndt, *Ber.*, **91**, 2167 (1958).

(25) F. Bohlmann, W. Weise, D. Rahtz and C. Arndt, *ibid.*, **91**, 2176 (1958).

(26) Complete infrared spectral curves are reproduced in the Ph.D. thesis of W. K. Musker, University of Illinois, 1959.

(27) N. J. Leonard and D. F. Morrow, THIS JOURNAL, **80**, 371 (1958).

(28) S. P. Findlay, *ibid.*, **75**, 4624 (1953).

(29) L. W. Haynes, University of Illinois, work in progress.

(30) Reference 4, see footnote 46 and Experimental for compound and for the name used earlier.

TABLE I

AMINOALCOHOLS USED IN MERCURIC ACETATE OXIDATIONS

Compound	B.p. °C.	B.p. Mm.	n^tD	°C.	Ref.	Derivative	M.p., °C.	Ref.
2-Pyrrolidinoethanol	78–79	18	1.4703	25	34	Bz-HCl[a]	174	33
2-Pyrrolidinopropanol	93–96	16	1.4755	25	35			
3-Pyrrolidinopropanol	100–101	15	1.4704	25	36	Bz-HCl	128.5–129.5	37
2-Piperidinoethanol	95–96	20	1.4775	25	38	Bz-HCl	172–173.5	33
2-(2′-Methylpiperidino)-ethanol	96–98	12	1.4779	25	12	Picrate	105.5–106.5	39
2-(3′-Methylpiperidino)-ethanol	98–100	16	1.4698	27	7	Picrate	139–140	7
2-(4′-Phenylpiperidino)-ethanol	104–108	0.1	1.5442	24	..	Bz-HCl	183–186 d.	..
2-(2′,6′-Dimethylpiperidino)-ethanol	114	12	1.4819	25	39	Picrate	142–143	39
3-Piperidinopropanol	114	19	1.4731	25	32	Bz-HCl	186–188	33
3-(2′-Methylpiperidino)-propanol	119–120	17	1.4771	25	12	Bz-HCl	171–172	32
3-(2′,6′-Dimethylpiperidino)-propanol	136	18	1.4819	25	40	Bz-HCl	165–166	40
3-(3′,5′-Dimethylpiperidino)-propanol	114	13	1.4659	25	..	Bz-HCl	200°	..
2-(2′,6′-Dimethylpiperidino)-1-phenylethanol	116[b]	0.3				HCl	240.5 d.	

[a] Benzoate hydrochloride. [b] M.p. 69–72°.

In conclusion, this general oxidative cyclization of aminoalcohols represents one of a series of possible ring closures wherein a nucleophilic group (hydroxyl, amino, enolic, aromatic or heteroaromatic type, etc.) combines with an iminium salt grouping ($>C{=}\overset{+}{N}<$) contained in the same molecule, as the latter is formed by the oxidation of a tertiary amine center.

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Experimental[31]

3-Piperidinopropanol.—By an adaptation of the method of Clinton, Salvador and Laskowski,[12] 47.5 g. (0.50 mole) of trimethylene chlorohydrin was added to a stirred solution of 85.0 g. (1 mole) of piperidine and 3.5 g. of sodium iodide in 104 ml. of absolute ethanol. After the solution was refluxed for 24 hours and cooled to room temperature, a solution of 11.5 g. (0.5 mole) of sodium in 200 ml. of absolute ethanol was added with stirring. The precipitated sodium chloride was filtered and washed several times with ether. The filtrate was distilled at atmospheric pressure to remove ether, ethanol and the excess piperidine. The residue was diluted to three times its volume with ether and filtered. The ethereal solution was dried, filtered, concentrated and distilled through a small Vigreux column to give 59.9 g. (84%) of 3-piperidinopropanol, b.p. 114° (19 mm.), n^{25}D 1.4731 (reported[32] 93–95° (9 mm.), n^{25}D 1.4755).

The benzoate hydrochloride was prepared by the method of von Braun, Braunsdorf and Rath.[33] Equimolar quantities of benzoyl chloride and 3-piperidinopropanol were separately dissolved in chloroform, mixed together and heated to reflux. The colorless benzoate hydrochloride which separated when ether was added to the solution was recrystallized from isopropyl alcohol as colorless needles, m.p. 186–188° (reported[33] 185°). The aminoalcohols (and their derivatives) which were used in the oxidation study are listed in Table I.

Mercuric Acetate Oxidation of 3-Piperidinopropanol. General Procedure.—A solution of 21.48 g. (0.15 mole) of 3-piperidinopropanol and 238.5 g. (0.75 mole) of mercuric acetate in 622 ml. of 5% acetic acid (95% water) was allowed to stand at room temperature for 78 days. The precipitated mercurous acetate was filtered, washed with dilute acetic acid (washings added to filtrate), then with acetone (washings discarded). The precipitate, dried by suction on the filter, weighed 73.2 g. (94% based on a two electron oxidation). The aqueous solution was saturated with hydrogen sulfide and the precipitated mercuric sulfide was removed by filtering the solution through a previously formed mat of wet Filter-Cel over a filter paper in a Büchner funnel. The precipitate was washed with dilute acetic acid and with water. The filtrate was then basified with solid potassium carbonate, added in small portions, while cooling in an ice-bath. When the evolution of carbon dioxide had ceased, a layer of ether was added and the aqueous layer was thoroughly saturated with potassium carbonate. The layers were separated, and the aqueous layer was extracted several times with ether. The combined ether extracts were dried over magnesium sulfate and filtered. The dried ether extracts were distilled in the Holzman column to give 5.32 g. (25%) of crude 5-oxa-1-azabicyclo[4.4.0]decane (VIIa) (36% conversion), and 4.31 g. (18%) of 1-(3′-hydroxypropyl)-2-piperidone (XIV).

The infrared spectrum of the crude tetrahydro-1,3-oxazine indicated that some starting material and some enamine or amidoalcohol were present in small amounts for it showed weak broad absorption bands at 3400 cm.$^{-1}$ and 1625–1650 cm.$^{-1}$. Vapor phase chromatography confirmed the presence of the aminoalcohol and also indicated another impurity which may be a small amount of enamine.

Redistillation of the crude tetrahydro-1,3-oxazine gave pure **5-oxa-1-azabicyclo[4.4.0]decane**, b.p. 87° (18 mm.), n^{25}D 1.4750, $\nu_{max}^{CCl_4}$ 2700–2800 and 1000–1200 cm.$^{-1}$ regions.

Anal. Calcd. for $C_9H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 67.83; H, 10.91; N, 9.68

The picrate was prepared by adding a saturated solution of picric acid in ethanol to a dilute solution of the base dissolved in ether. The salt was collected by filtration and recrystallized from ethyl acetate–hexane as yellow needles, m.p. 106.8–108° dec.

Anal. Calcd. for $C_{14}H_{18}N_4O_7$: C, 45.40; H, 4.90; N, 15.13. Found: C, 45.82; H, 4.91; N, 15.06.

The infrared spectrum (Nujol) showed no absorption bands in the $>C{=}N^+<$ or O—H region, indicating that the salt exists in the closed form XVI. The new bicyclic compounds and their picrates are listed in Table II.

(31) All melting points and boiling points are uncorrected. We are indebted to Miss Claire Higham, Miss Jane Liu and Mr. Josef Nemeth for the microanalyses. We also would like to thank Miss Mary Demott and Mr. Paul McMahon for the infrared absorption spectra.

The vapor fractometer which was used was a Perkin–Elmer model 154B. In all analyses a 6-foot silicone column was used and was heated to *ca.* 140°. Helium was used as the carrier gas at a flow rate of about 80 cc./min. at 70°F.

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TABLE II

FUSED OXAZOLIDINES AND TETRAHYDRO-1,3 OXAZINES

Product	Conversion, %	B.p. °C.	B.p. Mm.	n^tD	t, °C.	Derivative	M.p., °C.	State
A. By mercuric acetate oxidation of aminoalcohols								
4-Oxa-1-azabicyclo[3.3.0]octane (Xa)	27	52	15	1.4682	25	Picrate	79–80	Closed
2-Methyl-4-oxa-1-azabicyclo[3.3.0]octane (Xb)	22	53	11	1.4555	25	Picrate	95–96.5	Closed
5-Oxa-1-azabicyclo[4.3.0]nonane (IX)	37	60–61	14	1.4673	25	Picrate	104.5–105	Closed
7-Oxa-1-azabicyclo[4.3.0]nonane (VIIIa)	47	65–67	12	1.4705	24.5	None		
6-Methyl-7-oxa-1-azabicyclo[4.3.0]nonane (VIIIb)	66	75	18	1.4675	24	Picrate	76.5–78	Open
2,6-Dimethyl-7-oxa-1-azabicyclo[4.3.0]nonane (VIIIc)	75	84	18	1.4670	24	Picrate	150–154	Open
5-Oxa-1-azabicyclo[4.4.0]decane (VIIa)	36	87	18	1.4750	25	Picrate	106–108	Closed
6(10)-Methyl-5-oxa-1-azabicyclo[4.4.0]decane (VIIb mainly)	63	91	15	1.4782	24	Picrate	81.5–83.5	Closed
6,10-Dimethyl-5-oxa-1-azabicyclo[4.4.0]decane (VIIc)	65	105	12	1.4709	25	Picrate	93–94	Open
B. By sodium and butanol reduction of amidoalcohol								
Product	Yield, %							
5-Methyl-7-oxa-1-azabicyclo[4.3.0]nonane (XX)[7]	66	81–84	24	1.4667	24.5	Picrate	94–95	Open

An attempt was made to form trinitrobenzene and tetranitrofluorenone adducts of the bicyclic tetrahydro-1,3-oxazine in glacial acetic acid, ethanol, methanol and benzene. A deep red color developed when the reactants were mixed and heated, but on cooling only amorphous, non-crystallizable material could be obtained.

The presence of recovered 3-piperidinopropanol in the distillate was confirmed by the formation of a benzoate hydrochloride in 91% yield which showed no depression of its melting point on admixture with authentic 3-piperidinopropyl benzoate hydrochloride.

The high-boiling fraction was shown to be **1-(3′-hydroxypropyl)-2-piperidone** by analysis and by comparison with an authentic sample prepared by Middleton,[15] b.p. 138–139° (1.25 mm.), $n^{25.3}$D 1.4949 (reported[15] b.p. 155° (1.5 mm.), n^{20}D 1.4983); $\nu_{max}^{CHCl_3}$ 1620 and 1500 cm.$^{-1}$ (lactam), 3400 cm.$^{-1}$ (O–H).

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.57; H, 9.68; N, 8.68.

The 2,3-tetramethylene-5,6-dihydro-1,3,4-oxazinium perchlorate (XV) was formed by adding a solution of 50% perchloric acid–50% ethanol to an ethereal solution of the amidoalcohol. The product which separated was recrystallized as colorless needles from ethanol, after one recrystallization, m.p. 178–179° (reported[15] m.p. 185°), ν_{max}^{Nujol} 1672 cm.$^{-1}$ (>C=N$^+$<).

Preparation of 1-(3′-Hydroxypropyl)-2-piperidone.[15]—A solution of 23.0 g. (0.15 mole) of 1-(3′-hydroxypropyl)-2-pyridone in 50 ml. of absolute alcohol was reduced with hydrogen in the presence of 20 g. of Raney nickel. After 4 hours at room temperature, the theoretical amount of hydrogen had been absorbed. The solution was filtered, the filtrate was concentrated, and the residue was distilled under reduced pressure to give 21 g. (89%) of 1-(3′-hydroxypropyl)-2-piperidone, b.p. 155–158° (1.0–1.5 mm.), n^{20}D 1.4983.

The 2,3-tetramethylene-5,6-dihydro-1,3,4-oxazinium perchlorate was formed and was recrystallized from ethanol as colorless plates, m.p. 185–186°, ν_{max}^{Nujol} 1672 cm.$^{-1}$ (>C=N$^+$<).

Anal. Calcd. for $C_8H_{14}ClNO_5$: C, 40.09; H, 5.89; N, 5.85. Found: C, 40.16; H, 5.91; N, 5.78.

Mercuric Acetic Oxidation of 5-Oxa-1-azabicyclo[4.4.0]decane.—The oxidation of 0.72 g. (0.0051 mole) of 5-oxa-1-azabicyclo[4.4.0]decane with mercuric acetate yielded 0.26 g. (33%) of crude 1-(3′-hydroxypropyl)-piperidone. The infrared spectrum was nearly identical with the spectrum of authentic 1-(3′-hydroxypropyl)-2-piperidone.

Mercuric Acetate Oxidation of 3-(2′-Methylpiperidino)-propanol.—The oxidation of 15.73 g. (0.1 mole) of 3-(2′-methylpiperidino)-propanol with mercuric acetate was carried out at 60–65° for 18 hours. The total amount of mercurous acetate formed in this time was 40.7 g. (79%). The reaction was worked up in the usual way and yielded 8.66 g. (56%) of the crude tetrahydro-1,3-oxazine (64% conversion). No high-boiling products were isolated under these conditions.

Vapor phase chromatography of the product showed three peaks: one was shown to be 3-(2′-methylpiperidino)-propanol while the other two can be assumed to be **6-methyl-5-oxa-1-azabicyclo[4.4.0]decane (VIIb)** and **10-methyl-5-oxa-1-azabicyclo[4.4.0]decane (VII, R=H, R′=CH$_3$)**, with the former presumably predominating by a factor of nine. Distillation of the crude tetrahydro-1,3-oxazine gave the same mixtures of isomers, as indicated by vapor phase chromatography, b.p. 91° (15 mm.), n^{24}D 1.4782, $\nu_{max}^{CCl_4}$ 2700–2800 cm.$^{-1}$ and 1000–1200 cm.$^{-1}$ regions.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.94; H, 11.01; N, 8.97.

The picrate was formed in ether and was recrystallized from absolute ethanol as yellow needles, m.p. 81.5–83.5° dec. The infrared spectrum (Nujol) showed no absorption in the 3 and 6μ regions.

Anal. Calcd. for $C_{25}H_{20}N_4O_7$: C, 46.87; H, 5.25; N, 14.58. Found: C, 47.14; H, 5.06; N, 14.43.

Higher Temperature (95°) Mercuric Acetate Oxidation of 3-(2′-Methylpiperidino)-propanol.—The oxidation of 14.95 g. (0.95 mole) of 3-(2′-methylpiperidino)-propanol with mercuric acetate was performed at 95–98° for 2 hours. The total amount of mercurous acetate formed in this time was 42.7 g. (86%). The oxidation was continued for another 5 hours at 95° and although no additional mercurous acetate was formed, a small amount of mercury (1.04 g.) was found in the flask. The solution developed a deep yellow color during the course of the reaction. The reaction was worked up in the usual way yielding 8.34 g. (57%) of the crude mixture of 6-methyl- and 10-methyl-5-oxa-1-azabicyclo[4.4.0]decanes (in about the same ratio as in the milder oxidation) and 0.76 g. of a mixture of amidoalcohol and amidoester,[4] b.p. 126° (0.1 mm.), n^{21}D 1.4910. The infrared spectrum of the mixture showed absorption at 3380 cm.$^{-1}$ (O—H), 1738 cm.$^{-1}$ (acetate C=O) and 1620 and 1475 cm.$^{-1}$ (6-membered lactam). A wide shoulder at *ca.* 1675 cm.$^{-1}$ may indicate the presence of a small amount of enamine.

Mercuric Acetate Oxidation of 3-(2′,6′-Dimethylpiperidino)-propanol.—The oxidation of 8.7 g. (0.05 mole) of 3-(2′,6′-dimethylpiperidino)-propanol with mercuric acetate was carried out at 76° for 18.5 hours. The total amount of mercurous acetate formed in this time was 21.2 g. (82%). By the usual procedure the product was isolated and after distillation through a Holzman column, 5.03 g. (60%) of the crude tetrahydro-1,3-oxazine (65% conversion) was obtained.

Redistillation of the crude sample from sodium gave a mixture of the two stereoisomers of **6,10-dimethyl-5-oxa-1-azabicyclo[4.4.0]decane (VIIc)** in a ratio of about 20:1 as indicated by vapor phase chromatography, b.p. 105° (12 mm.), n^{25}D 1.4709, $\nu_{max}^{CCl_4}$ 1000–1200 cm.$^{-1}$ region.

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.96; H, 11.32; N, 8.28. Found: C, 70.81; H, 11.27; N, 8.46.

The picrate was formed in ether and was recrystallized from methanol–ether as yellow needles, m.p. 93–94.5° dec., ν_{max}^{Nujol} 1660 (>C=N$^+$<) and 3380 cm.$^{-1}$ (O—H).

Anal. Calcd. for $C_{16}H_{22}N_4O_7$: C, 48.24; H, 5.57; N, 14.07. Found: C, 47.96; H, 5.32; N, 14.12.

3-(3',5'-Dimethylpiperidino)-propanol (XVII).—The alkylation of 9.97 g. (0.88 mole) of 3,5-dimethylpiperidine with 4.24 g. (0.45 mole) of trimethylene chlorohydrin by the usual procedure yielded 4.36 g. (58%) of 3-(3',5'-dimethylpiperidino)-propanol, b.p. 114° (13 mm.), $n^{25}D$ 1.4659.

Anal. Calcd. for $C_{10}H_{21}NO$: C, 70.12; H, 12.36; N, 8.18. Found: C, 69.02; H, 12.43; N, 8.09.

The benzoate hydrochloride was prepared in the usual way and was recrystallized from acetone as colorless needles, m.p. 200°.

Anal. Calcd. for $C_{17}H_{26}ClNO_2$: C, 65.47; H, 8.45; N, 4.49. Found: C, 65.29; H, 8.53; N, 4.55.

Mercuric Acetate Oxidation of 3-(3',5'-Dimethylpiperidino)-propanol.—The oxidation of 3.2 g. (0.019 mole) of 3-(3',5'-dimethylpiperidino)-propanol with mercuric acetate was carried out at room temperature during 13 days. The total amount of mercurous acetate formed in this time was 9.04 g. (92%). The reaction, which was worked up in the usual way, yielded 1.18 g. (34%) of **1-(3'-hydroxypropyl)-3,5-dimethyl-2-piperidone (XVIII)** (54% conversion), b.p. 187° (11 mm.), $n^{26}D$ 1.4810; ν_{max}^{film} 1615 and 1492 cm.$^{-1}$ (lactam), 3360 cm.$^{-1}$ (O-H). No trace of bicyclic tetrahydro-1,3-oxazine was found.

Anal. Calcd. for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.90; H, 10.35; N, 7.33.

The reaction between the amidoalcohol and perchloric acid in isopropyl alcohol, in an attempt at ring closure, could not be effected even when the reactants were heated at reflux for 24 hours.

Mercuric Acetate Oxidation of 2-Piperidinoethanol.—The oxidation of 12.90 g. (0.1 mole) of 2-piperidinoethanol with mercuric acetate was effected at room temperature during 143 days. The total amount of mercurous acetate formed in this time was 52.1 g. (*ca.* 100%). The product was worked up in the usual manner and distilled through a Holzman column to give 6.00 g. (47%) of crude 7-oxa-1-azabicyclo[4.3.0]nonane (VIIIa), and 0.67 g. of a mixture of 1-(2'-hydroxyethyl)-2-piperidone and 1-(2'-acetoxyethyl)-2-piperidone, b.p. 138–150° (1 mm.), $n^{25}D$ 1.5039–1.5084. The infrared spectrum of the mixture of piperidones showed absorption maxima at 1625 (broad) and 1500 cm.$^{-1}$ (6-membered lactam), 3400 cm.$^{-1}$ (O—H stretching) and 1742 cm.$^{-1}$ (acetate C=O stretching). A small amount of 2-piperidinoethanol was present in the oxazolidine fraction as indicated by the presence of weak O-H absorption in the infrared spectrum and a weak intensity signal in vapor phase chromatography. The presence of enamine grouping was also indicated since the infrared spectrum showed a weak band at 1650 cm.$^{-1}$.

Crude **7-oxa-1-azabicyclo[4.3.0]nonane (VIIIa)** was redistilled several times through a Holzman column to give the pure but unstable oxazolidine, b.p. 65–67° (12 mm.), $n^{24.5}D$ 1.4705, $\nu_{max}^{CCl_4}$ 2700–2800 cm.$^{-1}$ and 1000–1200 cm.$^{-1}$ regions. Vapor phase chromatography showed the analytical sample to be homogeneous.

Anal. Calcd. for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.01. Found: C, 65.65, 65.97; H, 10.20, 10.02; N, 11.31.

When the oxazolidine was exposed to the air for a short period of time, the infrared spectrum began to show a band at 1655 cm.$^{-1}$ due to enamine absorption, and subsequently the entire sample turned to a dark red viscous tar. Complete absence of air and moisture will retard this decomposition. No stable derivative of the 7-oxa-1-azabicyclo[4.3.0]nonane could be prepared. Both the picrate and picrolonate decomposed upon contact with air.

Reduction of 7-Oxa-1-azabicyclo[4.3.0]nonane (VIIIa) with Lithium Aluminum Hydride.[41]—A solution of 0.1 g. of lithium aluminum hydride in 15 ml. of absolute ether was heated to reflux, and an ether solution of 0.29 g. (2.28 mmoles) of 7-oxa-1-azabicyclo[4.3.0]nonane was added at a rate necessary to maintain reflux. The solution was then heated at reflux for 20 hours and cooled. Water was added slowly until all of the hydride was decomposed, and the resulting solution was filtered. Five ml. of chloroform was added to the filtrate, and the ether was distilled. After 0.3 g. (2.15 mmoles) of benzoyl chloride was added to the chloroform solution, the product was precipitated by the addition of ether to give 0.43 g. (70%) of **2-piperidinoethyl benzoate hydrochloride**, m.p. 172–173.5°. No depression of the melting point was found on admixture with the authentic benzoate hydrochloride.

Mercuric Acetate Oxidation of 2-(2'-Methylpiperidino)-ethanol.—The oxidation of 14.32 g. (0.1 mole) of 2-(2'-methylpiperidino)-ethanol with mercuric acetate was performed at *ca.* 65° for 11 hours. The total amount of mercurous acetate formed in this time was 42.3 g. (82%). The basic products were isolated in the usual way and upon distillation yielded 8.14 g. (58%) of crude 6-methyl-7-oxa-1-azabicyclo[4.3.0]nonane (66% conversion). No high-boiling products were obtained. A representative sample of the oxazolidine was subjected to vapor phase chromatography and was found to contain a small amount of the aminoalcohol and a trace of the 2-methyl isomer.

Redistillation of the oxazolidine gave pure **6-methyl-7-oxa-1-azabicyclo[4.3.0]nonane (VIIIb)**, b.p. 75° (18 mm.), $n^{24}D$ 1.4675.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 67.84; H, 10.67; N, 9.64.

Vapor phase chromatography of the analytical sample showed only one peak. The infrared spectrum (10% in carbon tetrachloride) failed to show any hydroxyl or carbonyl absorptions. The characteristic oxazolidine bands were present in the 1000–1200 cm.$^{-1}$ region, but no multiplet of bands was observed in the 2700–2800 cm.$^{-1}$ region.

The picrate was prepared in ether and was recrystallized from absolute ethanol as yellow plates, m.p. 76.5–78° dec., ν_{max}^{Nujol} 1675 (>C=N$^+$<) and 3460 cm.$^{-1}$ (O—H).

Anal. Calcd. for $C_{14}H_{18}N_4O_7$: C, 45.40; H, 4.90; N, 15.13. Found: C, 45.64; H, 4.93; N, 14.98.

Higher (95°) Temperature Mercuric Acetate Oxidation of 2-(2'-Methylpiperidino)-ethanol.—The oxidation of 13.33 g. (0.093 mole) of 2-(2'-methylpiperidino)-ethanol with mercuric acetate was carried out at 95° for 4 hours and gave 48.85 g. (101%) of mercurous acetate. The usual work-up procedure gave 8.51 g. (65%) of crude 6-methyl-7-oxa-1-azabicyclo[4.3.0]nonane and 0.50 g. of a mixture of amidoester and amidoalcohol, b.p. 109–112° (0.15 mm.), $n^{24.6}D$ 1.4942. The infrared spectrum of the mixed amides was similar to the spectrum of the mixed amides from 2-piperidinoethanol.

Mercuric Acetate Oxidation of 2-(3'-Methylpiperidino)-ethanol.—The mercuric acetate oxidation of 4.45 g. (0.311 mole) of 2-(3'-methylpiperidino)-ethanol was carried out at room temperature for 29 days and yielded 12.91 g. (80%) of mercurous acetate. The products were worked up in the usual way and gave 2.52 g. of a mixture of oxazolidine, enamine alcohol and aminoalcohol, b.p. 95–112° (26 mm.), and 0.53 g. of a mixture of amidoalcohol and amidoester, b.p. 192° (26 mm.), $n^{25}D$ 1.4912.

The low-boiling fraction, which was tested by vapor phase chromatography, exhibited peaks corresponding to starting material and oxazolidine. (The oxazolidine used for comparison was synthesized by Sauers[7] by reducing 1-(2'-hydroxyethyl)-3-methyl-2-piperidone with sodium and butanol.) The infrared spectrum showed intense maxima at 1655 cm.$^{-1}$ (enamine) and 3400 cm.$^{-1}$ (hydroxyl). All attempts to purify the oxazolidine by distillation failed. The infrared spectrum of the high-boiling fraction showed absorption maxima at 3380 (O—H stretching), 1723 (ester C=O stretching), and 1610 and 1490 cm.$^{-1}$ (6-membered lactam absorption).

Mercuric Acetate Oxidation of 2-(2',6'-Dimethylpiperidino)-ethanol.—The oxidation of 15.73 g. (0.1 mole) of 2-(2',6'-dimethylpiperidino)-propanol with mercuric acetate was carried out at 65° for 40 hours. The total amount of mercurous acetate formed in this time was 42.7 g. (82%). The basic products were isolated in the usual way and upon distillation gave 10.51 g. (68%) of crude 2,6-dimethyl-7-oxa-1-azabicyclo[4.3.0]nonane (75% conversion). No high-boiling products were obtained. Vapor phase chromatography of the sample showed only a trace of starting material contaminating the product. Redistillation of the oxazolidine gave pure **2,6-dimethyl-7-oxa-1-azabicyclo[4.3.0]nonane (VIIIc)**, b.p. 84° (18 mm.), $n^{24}D$ 1.4670.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.59; H, 11.07; N, 9.21.

Vapor phase chromatography showed that the sample was homogeneous. The infrared spectrum (10% in carbon

(41) N. G. Gaylord, *Experientia*, 10, 351 (1954).

tetrachloride) failed to show any hydroxyl or carbonyl absorption. The characteristic oxazolidine bands were present in the 1000–1200 cm.$^{-1}$ region but there was no absorption in the 2700–2800 cm.$^{-1}$ region.

The picrate was formed in ether and was recrystallized as small yellow needles from absolute ethanol, m.p. 150–154°, ν_{max}^{Nujol} 1665 (>C=N$^+$<) and 3360 cm.$^{-1}$ (O—H).

Anal. Calcd. for $C_{15}H_{20}N_4O_7$: C, 46.87; H, 5.25; O, 33.30. Found: C, 46.73; H, 5.28; O, 33.37.

Mercuric Acetate Oxidation of 2-Pyrrolidinoethanol.—The oxidation of 11.53 g. (0.1 mole) of 2-pyrrolidinoethanol with mercuric acetate was carried out at 78° for 20 hours. The total amount of mercurous acetate formed in this time was 50.52 g. (97%). The product was worked up in the usual way; however, the solution turned a red color near the neutral point which became darker as the solution was basified. This red color was not extracted into the ether layer. The ether extracts were dried, filtered, concentrated and distilled to give 2.63 g. (23%) of crude 4-oxa-1-azabicyclo[3.3.0] octane (27% conversion). Trace amounts of high-boiling material were obtained. The infrared spectrum of the high-boiling fraction showed absorption maxima which may indicate the presence of enamine, amidoalcohol and amidoester.

The crude oxazolidine was submitted to vapor phase chromatography and showed a trace amount of starting material. Successive distillation in the Holzman column gave the pure though unstable product, **4-oxa-1-azabicyclo-[3.3.0]octane (Xa)**, b.p. 52° (15 mm.), n^{25}D 1.4682. The infrared spectrum (10% in carbon tetrachloride) showed no absorption in the hydroxyl, enamine or 2700–2800 cm.$^{-1}$ regions. The fingerprint region is not as well resolved as in the bicyclononane and bicyclodecane series.

Anal. Calcd. for $C_6H_{11}NO$: C, 63.68; H, 9.80; N, 12.39. Found: C, 64.16; H, 9.76; N, 12.62.

The picrate was formed in ether as yellow prisms, m.p. 79–80°, but could not be recrystallized without decomposition. The infrared spectrum (Nujol) showed no absorption above 1650 cm.$^{-1}$ except the usual Nujol absorption in the 2800–3000 cm.$^{-1}$ region.

Anal. Calcd. for $C_{12}H_{14}N_4O_7$: C, 42.11; H, 4.12; N, 16.37. Found: C, 42.39; H, 4.02; N, 16.21.

Mercuric Acetate Oxidation of 2-Pyrrolidinopropanol.—The oxidation of 12.92 g. (0.1 mole of 2-pyrrolidinopropanol with mercuric acetate was carried out at *ca.* 65° for 14 hours. The total amount of mercurous acetate formed in this time was 40.0 g. (77%). The reaction was worked up in the usual way and yielded 1.84 g. (14%) of crude 2-methyl-4-oxa-1-azabicyclo[3.3.0]octane (22.5% conversion). Vapor phase chromatography of the crude product showed only a trace of starting material.

Redistillation of the crude oxazolidine gave the homogeneous (by v.p.c.) **2-methyl-4-oxa-1-azabicyclo[3.3.0]octane (Xb)**, b.p. 53° (11 mm.), n^{25}D 1.4555 ,$\nu_{max}^{CCl_4}$ 1000–1200 cm.$^{-1}$ region.

Anal. Calcd. for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.01. Found: C, 66.29; H, 10.32; N, 11.09.

The picrate was formed in ether as yellow plates and could not be recrystallized, m.p. 95–96.5° dec. The infrared spectrum (Nujol) showed no absorption bands in the O—H or >C=N$^+$< regions, indicating that the picrate exists in the closed form.

Anal. Calcd. for $C_{13}H_{16}N_4O_7$: C, 43.82; H, 4.53; N, 15.73. Found: C, 43.90; H, 4.39; N, 15.70.

Mercuric Acetate Oxidation of 3-Pyrrolidinopropanol.—The oxidation of 12.91 g. (0.1 mole) of 3-pyrrolidinopropanol with mercuric acetate was performed at 95° for 5 hours. The total amount of mercurous acetate formed in this time was 50.95 g. (98%). The reaction was worked up in the usual way to give 4.31 g. (34%) of crude 5-oxa-1-azabicyclo-[4.3.0]nonane (37% conversion), and 0.47 g. of high-boiling material. Vapor phase chromatography of the metoxazine showed only a trace of aminoalcohol.

The crude product was redistilled to give the chromatographically pure **5-oxa-1-azabicyclo[4.3.0]nonane (IX)**, b.p. 60–60.5° (14 mm.), n^{25}D 1.4673. The infrared spectrum (10% in carbon tetrachloride) showed no absorption in the enamine or hydroxyl regions. No multiplet of bands appeared in the 2700–2800 cm.$^{-1}$ region, but the characteristic bands appeared in the 1000–1200 cm.$^{-1}$ region.

Anal. Calcd. for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.01. Found: C, 66.06; H, 10.42; N, 10.75.

The picrate was formed in ether and was recrystallized from absolute ethanol as yellow needles, m.p. 104.5–105°. The infrared spectrum (Nujol) showed no absorption between 1650 and 2600 cm.$^{-1}$ or above 3000 cm.$^{-1}$, indicating that the picrate exists in the closed form.

Anal. Calcd. for $C_{13}H_{16}N_4O_7$: C, 43.82; H, 4.53; N, 15.73. Found: C, 43.86; H, 4.47; N, 15.85.

The infrared spectrum of the high-boiling fraction exhibited strong maxima at 1495 and 1665 cm.$^{-1}$ (5-membered lactam), 1737 cm.$^{-1}$ (ester C=O stretching) and 3410 cm.$^{-1}$ (O—H stretching) indicating a mixture of amidoalcohol and amidoester.

Mercuric Acetate Oxidation of 5-Oxa-1-azabicyclo[4.3.0] nonane (IX).—The mercuric acetate oxidation of 5-oxa-1-azabicyclo[4.3.0]nonane yielded a small amount of a mixture of amidoester and amidoalcohol. The infrared spectrum was almost identical to the infrared spectrum of the high-boiling material described above.

Lithium Aluminum Hydride Reduction of 5-Oxa-1-azabicyclo[4.3.0]nonane.—The reduction of 5-oxa-1-azabicyclo-[4.3.0]nonane was performed in the same way as described earlier for the reduction of 7-oxa-1-azabicyclo[4.3.0]nonane. The aminoalcohol was isolated as the benzoate hydrochloride, yield 90%. No depression of the melting point was observed on admixture with authentic 3-pyrrolidinopropyl benzoate hydrochloride.

2-(4'-Phenylpiperidino)-ethanol.—Ethylene oxide was slowly bubbled into a boiling solution of 28.90 g. (0.18 mole) of 4-phenylpiperidine[42] in 100 ml. of methanol until the theoretical amount (0.18 mole) of oxide had been absorbed. The methanol was removed under reduced pressure and the product was distilled in a small Vigreux column. The yield of **2-(4'-phenylpiperidino)-ethanol** was 32.22 g. (87%), b.p. 104–108° (0.1 mm.), n^{24}D 1.5442; ν_{max}^{film} 700, 1495, 1600 cm.$^{-1}$ (monosubstituted benzene) and 3400 cm.$^{-1}$ (O–H).

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82. Found: C, 75.95; H, 9.30; N, 6.94.

The benzoate hydrochloride was prepared in the usual way and was recrystallized from isopropyl alcohol as colorless plates, m.p. 183–186° dec.

Anal. Calcd. for $C_{20}H_{24}ClNO_2$: C, 69.45; H, 6.99; N, 4.05. Found: C, 69.51; H, 6.90; N, 4.11.

Mercuric Acetate Oxidation of 2-(4'-Phenylpiperidino)-ethanol.—The oxidation of 10.1 g. (0.049 mole) of 2-(4'-phenylpiperidino)-ethanol was performed at *ca.* 60° for 88 hours. The total amount of mercurous acetate formed in this time was 22.9 g. (90%). The reaction was worked up in the usual way to give 5.31 g. (51%) of crude 4-phenyl-7-oxa-1-azabicyclo[4.3.0]nonane. The product solidified on distillation. The infrared spectrum of the crude product showed a trace of absorption in the enamine and hydroxyl regions. The crude product could not be recrystallized due to its extreme solubility in all the solvents which were tried (pentane, cyclohexane, ethyl acetate, ether, chloroform and methanol).

2-(2'6'-Dimethylpiperidino)-1-phenylethanol.—The alkylation of 22.6 g. (0.2 mole) of 2,6-dimethylpiperidine with 24 g. (0.2 mole) of styrene oxide was carried out by an adaptation of the method of Buchwalter and Granatic.[14] The mixture of reagents was slowly heated to a temperature of 190° over a period of 5 hours and was held at this temperature for 2 hours longer. The solution was distilled, using a heat lamp to prevent solidification in the apparatus, to give 40.12 g. (86%) of **2-(2',6'-dimethylpiperidino)-1-phenylethanol**, b.p. 116° (0.3 mm.). The aminoalcohol was purified by sublimation at 60° (1 mm.) forming colorless needles, m.p. 69–72°.

Anal. Calcd. for $C_{15}H_{23}NO$: C, 77.20; H, 9.94; N, 6.00. Found: C, 77.11; H, 10.21; N, 6.13.

The hydrochloride was prepared by bubbling anhydrous hydrogen chloride into an ethereal solution of the aminoalcohol. The precipitate which separated was filtered and was recrystallized from isopropyl alcohol as colorless plates, m.p. 239–240.5° dec.

Anal. Calcd. for $C_{15}H_{24}ClNO$: C, 66.76; H, 8.96; N, 5.20. Found: C, 66.81; H, 8.77; N, 5.11.

(42) C. H. Schmidle and R. C. Mansfield, THIS JOURNAL, **77**, 4636 (1955).