form extract was washed, dried, and evaporated to give 129 mg. of crude product. Chromatography on acidic alumina with chloroform as eluent gave a main fraction yielding crystals of m.p. 174° (187–188° after drying) from ethanol. Recrystallization from benzene–ether gave product with m.p. 176°, but two more recrystallizations from ethanol raised this to 188°; ultraviolet spectrum (methanol): λ_{max} 217 mμ (34,800), 257 mμ (12,400), plateau 282 mμ (4000); infrared spectrum (chloroform): 2907s, 2198s, 1656s, 1605m, 1590m, 1484s, 1456s, 1379s, 1350m, 1316m, 1269s, 1143w, 1117w, 1087w, 1066m, 1047m, 967w, 945w, 897w, 860w. *Anal.* Calcd. for $C_{23}H_{31}O_2N_3$: C, 72.40; H, 8.19; N, 11.01; 2 C-Me, 7.89; 3 C-Me, 11.82. Found: C, 71.82; H, 8.41; N, 11.27; C-Me, 10.35, 10.3 (distilled sample).

WALTHAM 54, MASS.

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

A Study of Oxazolidine Ring Isomerization in Models of the Diterpenoid Alkaloids[1]

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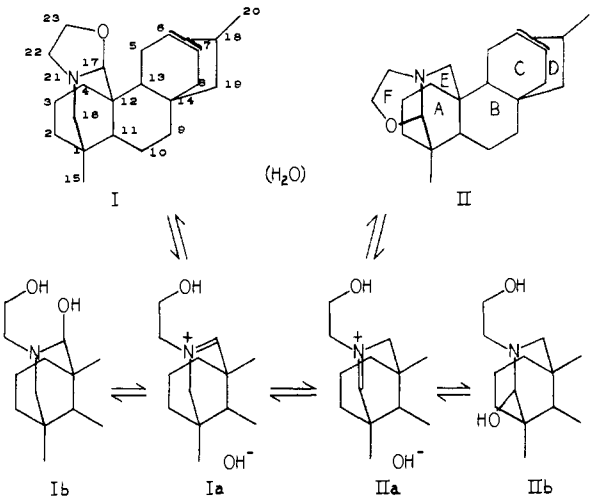
A tricyclic oxazolidine model of the A,E,F-ring system of the hexacyclic diterpenoid alkaloids has been constructed, namely, 6-aza-3-oxatricyclo[6.3.1.$0^{2,6}$]dodecane (III), in which there is no steric driving force to rearrangement of the oxazolidine ring. Isomerization of this model, which was found to require more strenuous conditions than the alkaloids (veatchine, atisine, cuauchichicine and garryfoline), was followed by means of deuterium incorporation (in deuterated solvents) and by loss of optical activity (using the resolved model). In another model system, of the arylaralkyloxazolidine type, in which there was no steric differentiation between the two α_N-carbons but in which the protons on these carbons were relatively more acidic than in the diterpenoid alkaloids and in the tricyclic oxazolidine, no isomerization occurred under the mild conditions which lead to the formation of the "iso" alkaloids. The original postulates of Wiesner relating to the basicity and isomerization of the diterpenoid alkaloids are supported by our findings. Incidental to these studies, we have found novelty of method in oxazolidine ring formation by means of mercuric acetate, and we have examined, in preliminary manner, the ring closure and ring opening of several oxazolinium compounds.

The alkaloids veatchine[5–10] (pK_a' 11.5),[11] atisine[10,12–20] (pK_a' 12.2),[11] cuauchichicine[21,22] (pK_a' 11.15) and garryfoline[21–23] (pK_a' 11.8) have in common the hexacyclic ring system I and differ only in the points of attachment of ring D and in the substituents on ring D. These alkaloids are readily isomerized, respectively, to garryine (pK_a' 8.7),[5] isoatisine (pK_a' 10.0[13] or 10.35[19]), isocuauchichicine (pK_a' 8.1)[22] and isogarryfoline (pK_a' 8.6),[22,23] represented by the isomeric oxazolidine II.



The conditions used for the isomerization are refluxing methanol (24 hours)[22,24] or refluxing 5% methanolic potassium hydroxide.[6,10] The greater basicity of the normal alkaloids compared with the "iso" alkaloids has been ascribed by Wiesner and Edwards,[10] in the former, to the higher proportion of the ternary iminium form Ia (quaternary Schiff base form) present in a possible equilibrium between the oxazolidine, ternary iminium form and pseudo base (I⇄Ia⇄Ib), and in the latter, to the higher proportion (in II⇄IIa⇄IIb) of the oxazolidine and pseudo base forms. The fundamental reason for the preponderance of form Ia in solution and for the isomerization within each alkaloid pair, proceeding through the ternary iminium form by prototropy (Ia→IIa), has been recognized as the steric inter-

(1) Presented in part at the 133rd National Meeting of the American Chemical Society, San Francisco, Calif., April 13–18, 1958.

(2) Monsanto Chemical Co. Fellow, 1956–1957; Ph.D. thesis, 1957.

(3) National Science Foundation Fellow, 1954–1955.

(4) Standard Oil Foundation Inc. (Indiana) Fellow, 1955–1956; Ph.D. thesis, 1956.

(5) K. Wiesner, S. K. Figdor, M. F. Bartlett and D. R. Henderson, *Can. J. Chem.*, **30**, 608 (1952).

(6) K. Wiesner, W. I. Taylor, S. K. Figdor, M. F. Bartlett, J. R. Armstrong and J. A. Edwards, *Chem. Ber.*, **86**, 800 (1953).

(7) M. F. Bartlett, W. I. Taylor and K. Wiesner, *Chemistry & Industry*, 173 (1953).

(8) M. F. Bartlett, J. Edwards, W. I. Taylor and K. Wiesner, *ibid.*, 323 (1953).

(9) K. Wiesner, R. Armstrong, M. F. Bartlett and J. A. Edwards, THIS JOURNAL, **76**, 6068 (1954).

(10) K. Wiesner and J. A. Edwards, *Experientia*, **11**, 255 (1955).

(11) Determined in 80% methyl Cellosolve–20% water, as were all the values except those of atisine and isoatisine (50% aqueous methanol).

(12) K. Wiesner, R. Armstrong, M. F. Bartlett and J. A. Edwards, *Chemistry & Industry*, 132 (1954).

(13) S. W. Pelletier and W. A. Jacobs, THIS JOURNAL, **76**, 4496 (1954).

(14) S. W. Pelletier and W. A. Jacobs, *ibid.*, **78**, 4139 (1956).

(15) S. W. Pelletier and W. A. Jacobs, *ibid.*, **78**, 4144 (1956).

(16) O. E. Edwards and Tara Singh, *Can. J. Chem.*, **33**, 448 (1955).

(17) D. Dvornik and O. E. Edwards, *Chemistry & Industry*, 248 (1956).

(18) D. Dvornik and O. E. Edwards, *Can. J. Chem.*, **35**, 860 (1957).

(19) S. W. Pelletier and W. A. Jacobs, *Chemistry & Industry*, 1385 (1955).

(20) Z. Valenta and K. Wiesner, *ibid.*, 354 (1956).

(21) C. Djerassi, C. R. Smith, S. K. Figdor, J. Herran and J. Romo, THIS JOURNAL, **76**, 5889 (1954).

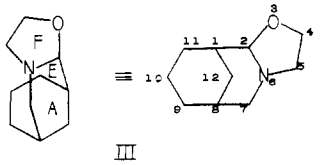
(22) C. Djerassi, C. R. Smith, A. E. Lippman, S. K. Figdor and J. Herran, *ibid.*, **77**, 4801 (1955).

(23) C. Djerassi, C. R. Smith, A. E. Lippmann, S. K. Figdor and J. Herran, *ibid.*, **77**, 6633 (1955).

(24) Prof. C. Djerassi (private communication) has indicated that a shorter period (6–8 hours) may be sufficient.

ference of ring C—particularly the C-5 hydrogens—with substituents on tetrahedral C-17 (greater interference than with trigonal C-17).[10,18,19,22]

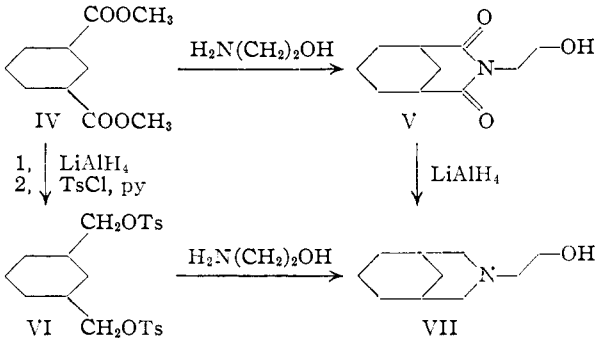
We have now constructed a simple model of the A,E,F-ring system of these diterpenoid alkaloids, namely, 6-aza-3-oxatricyclo[6.3.1.$0^{2,6}$]dodecane (III), in which there is no steric driving force to rearrangement of the oxazolidine ring. This model has served to define the stability toward isomerization and the base strength and other properties of the



III

tricyclic ring moiety (in I, II) when freed from the steric influence of the remaining rings of the diterpenoid alkaloids.

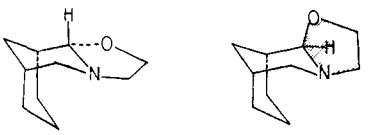
For the synthesis of 6-aza-3-oxatricyclo[6.3.1.$0^{2,6}$]-dodecane, 3-hydroxyethyl-3-azabicyclo[3.3.1]-nonane (VII) was required as a precursor. Compound VII was first prepared by the lithium aluminum hydride reduction (79% yield) of the imide V obtained (10% yield of pure imide) from dimethyl *cis*-1,3-cyclohexanedicarboxylate (IV) and monoethanolamine. An improved route (23% over-all yield) lay through the ditosylate VI of the mixture of *cis*- and *trans*-1,3-bis-hydroxymethylcyclohexane obtained by hydride reduction of the



mixed hexahydroisophthalates. Steam distillation afforded a clean separation of the desired product, 3-hydroxyethyl-3-azabicyclo[3.3.1]nonane. Syntheses of similar hetero-bicyclo[3.3.1]nonanes have been reported elsewhere.[25,26]

The oxidation of a 1,3,3-trialkylpiperidine with mercuric acetate in aqueous acetic acid solution at steam-bath temperature has been shown to give the corresponding 2-piperidone, along with the Δ^5-tetrahydropyridine.[27] The major product from the mercuric acetate oxidation of VII under similar conditions was thus expected to be 3-hydroxyethyl-2-keto-3-azabicyclo[3.3.1]nonane (X), since steric strain would not permit the location of a double bond at the bridgehead- or $\Delta^{2(1)}$-position (Bredt's rule).[28] The actual product exhibited infrared absorption maxima characteristic of the hydroxyl and the lactam carbonyl, but in addition a strong maximum at 1743 cm.$^{-1}$ indicative of an ester grouping. The assumption that the co-product with X was the corresponding acetate ester was confirmed when the mixture was converted by means of acetic anhydride to pure 3-acetoxyethyl-2-keto-3-azabicyclo[3.3.1]nonane (XI). Reduction of the mixture with sodium and butanol furnished 3-hydroxyethyl-2-keto-3-azabicyclo[3.3.1]nonane (X) in pure form, readily separable from the 3-hydroxyethyl-3-azabicyclo[3.3.1]nonane which was also produced, but apparently none of compound III.[29]

For successful ring closure of 3-hydroxyethyl-3-azabicyclo[3.3.1]nonane (VII) to the tricyclic oxazolidine III, we were guided to employ mercuric acetate oxidation at lower temperature (25°) by the over-oxidation experienced at 100° and by the observation that precipitation of mercurous acetate began even as the amine VII was being added to the oxidizing solution. After about 4.5 hours at 25°, the theoretical amount of mercurous acetate for a two-electron oxidation had been precipitated and pure 6-aza-3-oxatricyclo[6.3.1.$0^{2,6}$]dodecane (III) was isolated in 62% yield. *This conversion illustrates a new method of ring closure for the synthesis of oxazolidines*, the generality of which is being tested in this Laboratory. Different reagents have been used by Wiesner and others to effect similar ring closure in the alkaloid series: namely, osmium tetroxide in ether (dihydrogarryine → garryine,[8] and atisine partial synthesis[15]) and silver oxide in methanol (dihydronapelline → $C_{22}H_{33}NO_3$ and $C_{22}H_{35}NO_4$ compounds).[30] The new oxazolidine III was characterized by analysis, infrared spectrum and conversion products and was shown to be homogeneous by vapor phase chromatography.[31]



IIIa IIIb

The base strength of the oxazolidine was in the range of the "iso" alkaloids: pK_a' 8.35 (66% DMF), 9.03 (33% DMF), 9.45 (water), and of 3,5-diethyl-1-methyl-Δ^1-tetrahydropyridinium perchlorate[27]: pK_a' 8.46 (66% DMF), 9.47 (water). In the latter model, devoid of the alcohol function, reaction with hydroxyl ion can lead to ternary iminium hydroxide, pseudo base and enamine forms in equilibrium. While the bicyclic pseudo base and/or tricyclic oxazolidine forms of III are thus important contributors in aqueous solutions of the neutral material, at least a portion of the conjugate acid of III must be in the ternary iminium form IX since a solution in aqueous (D_2O) acid (DCl)

(25) G. A. Haggis and L. N. Owen, *J. Chem. Soc.*, 399 (1953).

(26) L. M. Rice and C. H. Grogan, Abstracts of Papers, American Chemical Society Meeting, San Francisco, Calif., April, 1958, p. 13M; *J. Org. Chem.* **23**, 844 (1958).

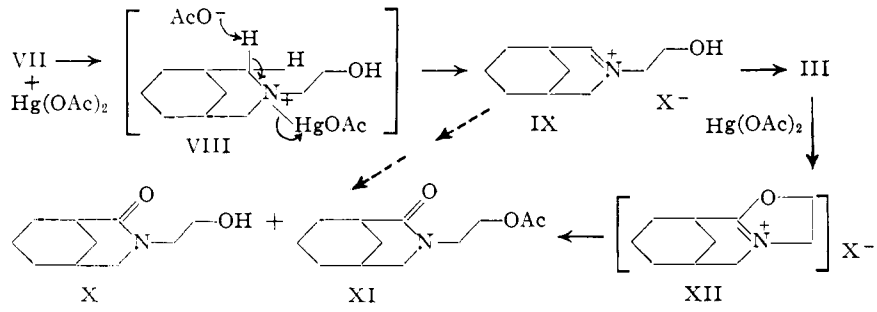
(27) N. J. Leonard and F. P. Hauck, Jr., THIS JOURNAL, **79**, 5279 (1957).

(28) F. S. Fawcett, *Chem. Revs.*, **47**, 219 (1950).

(29) By contrast, sodium and butanol reduction of 1-hydroxyethyl-3-methyl-2-piperidone effected ring closure to the corresponding oxazolidine, 2-methyl-6-aza-9-oxabicyclo[4.3.0]nonane, in 66% yield (see Experimental section, also footnote 46).

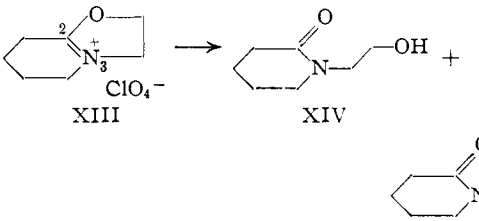
(30) K. Wiesner, Z. Valenta, J. F. King, R. K. Maudgal, L. C. Humber and Shô Itô, *Chemistry & Industry*, 173 (1957).

(31) At this stage, insufficient evidence is available to make a confident assignment of the relative stereochemistry (racemate corresponding to IIIa or IIIb) of the oxazolidine synthesized.



exhibited a strong infrared maximum at 1682 cm.$^{-1}$. The picrate of III also had an infrared maximum in this region (1685 cm.$^{-1}$) and one at 3340 cm.$^{-1}$ (Nujol), indicating that the solid is in the ternary iminium form IX.

Returning to the products of over-oxidation of 3-hydroxyethyl-3-azabicyclo[3.3.1]nonane (VII) with mercuric acetate before we consider the isomerization of the tricyclic oxazolidine III, two courses are open to the intermediate hydroxyethyl ternary iminium salt IX. The addition of water or acetic acid followed by loss of a proton would give the corresponding pseudo base (*cf.* IIa⇄IIb) or its acetate, which could again be oxidized by mercuric acetate on the same carbon to yield the 3-hydroxyethyl-2-keto-3-azabicyclo[3.3.1]-nonane (X).[32,33] Alternatively, intramolecular nucleophilic attack of the terminal hydroxyl on the carbon of the ternary iminium grouping[34] would furnish the tricyclic oxazolidine, which could then undergo further oxidation by mercuric acetate to the tricyclic oxazolinium compound XII. In view of the well-documented examples of attack by nucleophilic reagents on C-5 of the oxazoline (or oxazolinium salt) ring system,[35-40] it is reasonable to consider that acetate ion in the reaction medium acted as a nucleophile, opening the ring in XII to form 3-acetoxyethyl-2-keto-3-azabicyclo[3.3.1]nonane (XI). Attack of the intermediate XII by water at C-2 (or C-5) of the oxazolidine ring would account for the 3-hydroxyethyl-2-keto-3-azabicyclo[3.3.1]nonane (X) which was present in the product mixture. The formation of the acetate XI in the presence of the amount of water available under the mercuric acetate oxidation conditions was somewhat surprising in the light of the reported fast reaction of the oxazolinium salts with water.[35] For this reason we investigated the reaction of 2,3-tetramethylene-2-oxazolinium perchlorate (XIII)[41] with sodium acetate and 5% acetic acid in approximately the same concentrations as used in the mercuric acetate oxidations. The material isolated was a mixture of 1-acetoxyethyl- (XV) and 1-hydroxyethyl - 2 - piperidone (XIV), indicating that the acetate–acetic acid–water medium was sufficient to account for the parallel mixture, X and XI, obtained from the mercuric acetate oxidation of VIII with XII as the likely intermediate.[44] The product isolated from the reaction of XIII with sodium acetate in glacial acetic acid was mainly 1-acetoxyethyl-2-piperidone (XV), contaminated with some XIV; with potassium formate in ethanol, mainly 1-formoxyethyl-2-piperidone.



We may now consider the diterpenoid alkaloid isomerization (I → II) in the model 6-aza-3-oxatricyclo[6.3.1.$0^{2,6}$]dodecane (III) with sterically equivalent α_N-carbons (C-2 and C-7). The mechanism postulated[6,10] for the isomerization involves abstraction of a proton from the α_N-methylene carbon in ring E with simultaneous or subsequent addition of a proton at the original α_N-trigonal carbon. Whether the base (as in XVIII) is added alkali, solvent or simply the alkoxide[22] produced by heterolytic fission of the oxazolidine, the essential feature is unchanged, namely, that *this isomerization must be accompanied by loss and gain of a proton.*[45] It is therefore subject to study by deuterium exchange (XVIII, XIX, XX). When the tricyclic oxazolidine III was heated under reflux with methanol-*d* for 24 hours, conditions sufficient to effect the alkaloid isomerization (I → II), no

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

(33) N. J. Leonard and R. R. Sauers, *J. Org. Chem.*, **22**, 63 (1957).

(34) N. J. Leonard and A. S. Hay, THIS JOURNAL, **78**, 1984 (1956).

(35) S. Winstein and R. Boschan, *ibid.*, **72**, 4669 (1950).

(36) G. E. McCasland, R. K. Clark, Jr., and H. E. Carter, *ibid.*, **71**, 637 (1949).

(37) G. E. McCasland and D. A. Smith, *ibid.*, **72**, 2190 (1950).

(38) T. Taguchi and M. Kojima, *ibid.*, **78**, 1464 (1956).

(39) H. W. Heine, *ibid.*, **79**, 907 (1957).

(40) F. L. Scott, R. E. Glick and S. Winstein, *Experientia*, **13**, 183 (1957).

(41) Made very conveniently by heating 1-hydroxyethyl-2-piperidone (XIV) in ethanol with perchloric acid (*a general method*). This compound (XIII), the ring homolog 2,3-tetramethylene-5,6-dihydro-1,3,4-oxazinium perchlorate (XVI)[42] and $\Delta^{5(10)}$-dehydroquinolizidinium perchlorate (XVII) are all transparent in the ultraviolet region above 220 mμ in ethanol *when the solutions are freshly prepared.* These determinations cast doubt on the assignment by Edwards, Clarke and Douglas[43] of an ultraviolet maximum above 250 mμ to the >C=N⁺< grouping and suggest that the absorption observed in this region in at least two examples[19,43] may be due to materials formed during the aging of the spectrographic solutions.

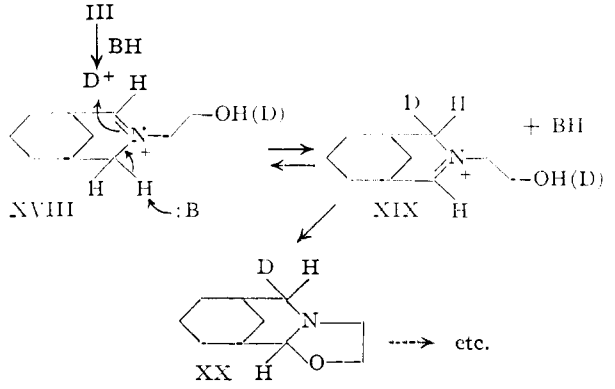
(42) O. Wintersteiner and M. Moore, THIS JOURNAL, **78**, 6193 (1956).

(43) O. E. Edwards, F. H. Clarke and B. Douglas, *Can. J. Chem.*, **32**, 235 (1954).

(44) These systems (XIII and (postulated) XII) are unusual in that the oxazolinium nitrogen does not bear a proton, and the increased rate of attack by acetate at sec.-C-5 over water at C-2 of the oxazoline ring may be due in part to this constitutional change from the examples which have been so thoroughly examined.[35-40]

(45) It should be noted that isomerization reversing the configuration of C-17 in I or of C-2 in III, involving nothing but heterolytic cleavage of the oxazolidine ring followed by reclosure from the opposite side of the ternary iminium system,[10] would not produce deuterium exchange.

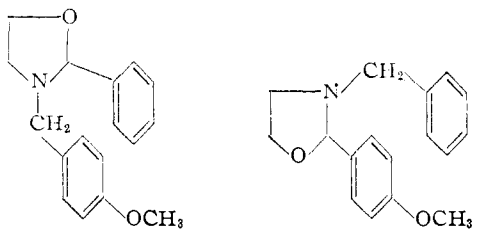
deuterium was incorporated in the product, which was identical with the original (III). In the presence of methanol-*d* and added base (sodium methoxide), after a 3-hour reflux period less than 5% of one hydrogen atom per molecule of III was exchanged by deuterium (infrared approximation).



When the solvent used was a mixture of dioxane and deuterium oxide (85°), a 24-hour reflux period resulted in the exchange of less than 30% of one hydrogen per molecule (deuterium analysis). Thus, more strenuous conditions were found to be necessary to effect the isomerization of the model III than the alkaloids I.[46]

Another study of the isomerization of the model compound (III) was made by means of optical activity. It will be noted that the tricyclic oxazolidine is an asymmetric compound and that isomerization of the type which has been postulated in the alkaloids would change III into its enantiomorph (over-all conversion, regardless of path: III → XX, for D read H). Therefore the resolution of the model compound and a study of its rate of racemization under the isomerizing conditions should give an additional estimate of the rate of isomerization in the model compound. A sample of optically active III, $[\alpha]^{25}D$ −52° (ethanol), was isolated as the free base by decomposition of the dibenzoyl-*d*-tartrate. No effort was made to obtain material of maximum optical activity due to the small size of the sample available. When the optically active material was held at 65° in ethanol, the activity was lost to the extent of about 30% in 24 hours. In racemization of optically pure material, the amount of isomerization would be one-half the amount of racemization, but since the active form of III which was used may not have been optically pure, 15% only approximates the extent of isomerization that occurred in the 24-hour period at 65°. We need not be concerned with the particular forms of III present in the ethanolic solution, since the isomerization is slow compared with the equilibration between the oxazolidine, pseudo base and ternary iminium forms and the composition of the equilibrium mixture will be identical for the enantiomorphs. The racemization results are qualitatively consistent with the deuterium exchange reactions. According to both findings, the steric interference of ring C would have to account for the (roughly) several hundredfold increase in the rate of isomerization (I → II).[10]

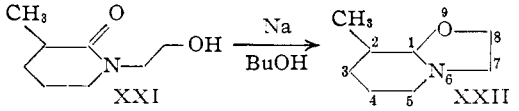
Another oxazolidine model, an arylaralkyloxazolidine type, was selected for study in which there was no steric differentiation between the two α_N-carbons but in which the protons on these carbons were relatively more acidic than in III and in I and II. The 2-phenyl-3-(*p*-methoxybenzyl)-oxazolidine (XXIII) was obtained in pure form by the condensation of benzaldehyde with 2-(*p*-methoxybenzylamino)-ethanol in benzene,[47] using a short period of heating and removing the water as formed. Hydrolysis of XXIII with 6 *N* hydrochloric acid at room temperature, followed by extraction and isolation of the basic material, returned the original aminoalcohol. 2-(*p*-Methoxyphenyl)-3-benzyloxazolidine (XXIV) was made in pure form from 2-(benzylamino)-ethanol and anisaldehyde. The initial aminoalcohol was isolated (97% recovery) following the controlled acid hydrolysis, confirming this method of product analysis.



XXIII XXIV

Each of the arylaralkyloxazolidines was subjected separately to the alkaloid isomerization (I → II) conditions, namely, refluxing in methanol for 24 hours. Neither XXIII nor XXIV underwent any appreciable change (*cf.* III with methanol-*d*), as followed by identification of each product through a controlled hydrolysis. By contrast, when either XXIII or XXIV was heated (193°) in diethylene glycol monomethyl ether under nitrogen for 24 hours, isomerization was observed, with the formation of a mixture of the two products in roughly equal amounts.[48,49] Here again, while isomerization may occur, the rate is much reduced from that observed for the diterpenoid alkaloids (I).

(46) A bicyclic model, 2-methyl-6-aza-9-oxabicyclo[4.3.0]nonane (XXII), showed less than 5% of one hydrogen per molecule exchanged



for deuterium during 2 hours in refluxing methanol-*d* and only about 5% exchanged during 23 hours in refluxing dioxane–deuterium oxide. The percentages were estimated from the C–D stretching region of the infrared spectra.

(47) E. D. Bergmann, *Chem. Revs.*, **53**, 309 (1953).

(48) This system offers an opportunity of studying the effect of different aryl substituents on the position of equilibrium, which R. R. S. proposes to investigate.

(49) F. Wegener, *Ann.*, **314**, 231 (1901), has demonstrated, among other cases, the interconvertibility of benzyl-*p*-nitroisobenzaldoxime and *p*-nitrobenzylisobenzaldoxime in the presence of hot sodium ethoxide. C. K. Ingold and C. W. Shoppee, *J. Chem. Soc.*, 1199 (1929), have shown that *p*-methoxybenzylidenebenzylamine and benzylidene-*p*-methoxybenzylamine both produce the same equilibrium mixture of the two compounds (79 and 21%, respectively) when heated at 85° in the presence of sodium ethoxide in ethanol. Similarly, benzaldehyde has been isolated from the reaction of dibenzylamine with formaldehyde. This indicates an isomerization from the methyleneamine to the benzylideneamine (H. T. Clark, H. B. Gillespie and S. Z Weisshaus, THIS JOURNAL, **55**, 4571 (1933)).

Finally, the prototropic isomerization of ternary iminium compounds is not a universal phenomenon but is highly dependent upon steric factors and upon the reaction conditions. Prototropy in such a system must be invoked with caution to explain structural changes,[50-52] unless steric interference on one side of the nitrogen provides an obvious driving force. As examples of ternary iminium compounds which give no evidence of isomerization under mild conditions we have provided the following: 4-methyl-Δ^4-dehydroquinolizidinium perchlorate and 4-methyl-$\Delta^{5(10)}$-dehydroquinolizidinium perchlorate,[53] 3-methyl-Δ^3-hexahydropyrrocolinium perchlorate and 3-methyl-$\Delta^{4(9)}$-hexahydropyrrocolinium perchlorate.

Experimental[54]

N-Hydroxyethyl-*cis*-1,3-cyclohexanedicarboximide (V).—A mixture of 6.6 g. (0.03 mole) of dimethyl *cis*-1,3-cyclohexanedicarboxylate,[26,55] obtained from *cis*-1,3-cyclohexanecarboxylic acid,[56] and 2.1 ml. (0.035 mole) of 2-aminoethanol was heated in an air-bath at 200° under a Holzman column,[57] with the column heater turned off. After 5 hours, 1.4 ml. (50% of theoretical) of methanol was collected. Vacuum was applied for 1 hour, the column heat was turned on, and distillation was effected. The fractions boiling between 136 and 149° (0.07 mm.) amounted to 1.64 g. (27% crude yield) and solidified on standing. Repeated recrystallizations from benzene–cyclohexane yielded pure N-hydroxyethyl-*cis*-1,3-cyclohexanedicarboximide as colorless platelets, m.p. 85–86°; ν_{max}^{Nujol} 3435 (O–H), 1665, 1720 cm.$^{-1}$ (imide C=O doublet).

Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67; N, 7.10. Found: C, 61.18; H, 7.42; N, 7.16.

Chromatography on acid-washed alumina was found to be useful for the separation of the cyclic imide from the linear material. The dark-colored oily by-products were eluted first from the column with benzene and the desired bicyclic material was collected from the later benzene fractions and the benzene–ether fractions.

The *p*-nitrobenzoate of N-hydroxyethyl-1,3-cyclohexanedicarboximide was obtained with *p*-nitrobenzoyl chloride and pyridine. After recrystallization from aqueous ethanol, the colorless microcrystalline substance melted at 144.8–145.2°.

Anal. Calcd. for $C_{17}H_{18}N_2O_6$: C, 58.95; H, 5.24; N, 8.09. Found: C, 59.12; H, 5.03; N, 8.10.

An attempt to carry out aminolysis of the mixed dimethyl 1,3-cyclohexanedicarboxylates in vigorously stirred, refluxing xylene during a 48-hour period led to recovery of 89% of the starting diester and about 3% of a colorless solid, m.p. 204–205° (from ethanol–ethyl acetate), which was assigned the structure **N,N-bis-hydroxyethyl-1,3-cyclohexanedicarboxamide** solely on the basis of the analysis.

Anal. Calcd. for $C_{12}H_{22}N_2O_4$: C, 55.79; H, 8.58; N, 10.85. Found: C, 56.04; H, 8.44; N, 10.67.

3-Hydroxyethyl-3-azabicyclo[3.3.1]nonane (VII).—(A) A solution of 6.4 g. (0.032 mole) of N-hydroxyethyl-*cis*-1,3-cyclohexanedicarboximide in 50 ml. of anhydrous benzene was added at a rate that just maintained gentle boiling to a stirred suspension of 4.1 g. of lithium aluminum hydride in 150 ml. of anhydrous ether. The mixture was heated under reflux for 4 hours. After destruction of the excess hydride, the mixture was steam distilled until 600 ml. of distillate had been collected. The layers of the distillate were separated, and the aqueous layer was extracted with chloroform. The combined organic phases were given a preliminary drying over magnesium sulfate, filtered, concentrated and distilled through the Holzman column, b.p. 123–125° (13 mm.), yield 4.36 g. (79%), $n^{25}D$ 1.4982–1.4987; ν_{max}^{film} 3400 (O–H), 2900, 2770 cm.$^{-1}$ (C–H).

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.28. Found: C, 70.91; H, 11.18; N, 8.07.

The picrate was formed in methanol and recrystallized from ethyl acetate containing a trace of ethanol as yellow prisms, m.p. 163.5–165.5°.

Anal. Calcd. for $C_{16}H_{22}N_4O_8$: C, 48.24; H, 5.57; N, 14.07. Found: C, 48.52; H, 5.46; N, 13.98.

The *p*-nitrobenzoate hydrochloride was prepared by warming a benzene solution of stoichiometric quantities of the bicyclic aminoethanol and *p*-nitrobenzoyl chloride on a steam-bath for 30 minutes and was recrystallized from methylene chloride–ethyl acetate or from ethanol–ethyl acetate as needles, m.p. 216.5–217.5°.

Anal. Calcd. for $C_{17}H_{23}ClN_2O_4$: C, 57.54; H, 6.53; N, 7.90. Found: C, 57.83; H, 6.69; N, 7.75.

(B) A mixture of 39.6 g. (0.085 mole) of the ditosylate of impure *cis*-1,3-bis-hydroxymethylcyclohexane[25] [needles, m.p. 71–75°; (reported[25] plates, m.p. 99–100°; *trans* isomer, plates, m.p. 86–87°); $\nu_{max}^{CHCl_3}$ (selected) 3050, 2940, 2870 (C–H), 1610, 1500 (arom.), 1365, 1195 and 1180 cm.$^{-1}$ (sulfonate ester bands), similar to spectrum of methyl *p*-toluenesulfonate] and 15.4 ml. (*ca.* 0.25 mole) of 2-aminoethanol in 1.15 l. of dry xylene was stirred and heated at reflux for 66 hours. The mixture was cooled and 200 ml. of water and 6 ml. of concentrated sulfuric acid were added. The acidic mixture was steam distilled until all the xylene had been removed. The residual solution was rendered basic with potassium carbonate and steam distilled again. The product, 3-hydroxyethyl-3-azabicyclo[3.3.1]nonane, separated in the distillate as an oil which was collected with the aid of a little ether and was redistilled through the Holzman column to give 9.05 g. (63%) of product, b.p. 122–128° (12–18 mm.), $n^{26}D$ 1.4980. A picrate prepared from this base had an identical melting point and mixture melting point with the picrate prepared from the base obtained by route A.

(C) To a suspension of 15 g. of lithium aluminum hydride in 350 ml. of tetrahydrofuran which had just been distilled from lithium aluminum hydride was added dropwise, at a rate that maintained reflux, while stirring and cooling in an ice-bath, 63.5 g. (0.317 mole) of dimethyl hexahydroisophthalate.[56] The addition required 15 minutes, after which the mixture was heated under reflux for 3 hours. Ethyl acetate, ethanol, water and 10% hydrochloric acid were added in that order to destroy the excess hydride. The resulting solution was extracted continuously with ether for 22 hours. The ether was removed, benzene was added and water was separated by means of a Dean–Stark trap. After removal of the benzene, the residual bis-hydroxymethylcyclohexane was distilled through the Holzman column to yield 43.3 g. (94%) of a viscous colorless oil, b.p. 109–116° (0.3 mm.), $n^{25}D$ 1.4807–1.4868. The diol was dissolved in 465 ml. of pyridine and cooled to ice temperature before 126 g. of *p*-toluenesulfonyl chloride was added. After 23 hours at about 3°, the mixture was poured into ice and water. The aqueous phase was removed by decantation and was extracted with benzene. The benzene extract was added to the original oily phase and the remaining traces of water were removed by the use of the Dean–Stark trap. The solution was concentrated, xylene was added, and the solution was concentrated again to ensure the removal of all traces of pyridine. A solution of this residue in 2.4 l. of dry xylene was treated with 54 ml. of 2-aminoethanol, followed by vigorous boiling and stirring under reflux for 45 hours. The 3-hydroxyethyl-3-azabicyclo[3.3.1]nonane was isolated from the reaction mixture as described in section B. The yield was 12.3 g. (23% from the mixed esters).

Mercuric Acetate Oxidation (100°) of 3-Hydroxyethyl-3-azabicyclo[3.3.1]nonane. Mixture of 3-Acetoxyethyl-(XI) and 3-Hydroxyethyl-2-keto-3-azabicyclo[3.3.1]nonane (X).—To a solution of 102.5 g. (0.32 mole) of mercuric acetate in 250 ml. of 5% acetic acid was added 9.05 g. (0.054 mole) of the bicyclic aminoethanol. A transient yellow color ap-

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(54) All melting points are corrected. We are indebted to Mrs. Maria Stingl, Miss Claire Higham and Mr. Josef Nemeth for the microanalyses. We also thank Mr. James Brader and Mr. Brian Clooney for the determination of the infrared absorption spectra.

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peared immediately. The mixture was warmed on the steam-bath, with stirring, for 4 hours. After cooling, the mercurous acetate was removed by filtration; yield 53.7 g. (96% of theoretical for four-electron oxidation). The filtrate was extracted with seven 25-ml. portions of chloroform. The extracts were concentrated and distilled through the Holzman column to give 8.30 g. of product, b.p. 131–136° (0.3 mm.), $n^{25}D$ 1.5050–1.5186; ν_{max}^{film} 3400 (O–H), 2920 and 2860 (C–H), 1743 (acetate C=O) and 1620 cm.$^{-1}$ (amide C=O). A small amount of metallic mercury codistilled with the product.

3-Acetoxyethyl-2-keto-3-azabicyclo[3.3.1]nonane (XI).—A solution of 1.46 g. of the mixed amido-alcohol and acetate (see above) in 5 ml. of pyridine was cooled to 0° and 1.0 ml. of acetic anhydride was added. After being maintained for 2 hours at 0°, the mixture was treated with water to destroy the excess anhydride. Ether was added, and the ether layer was extracted in sequence with 10% hydrochloric acid, water, 10% sodium bicarbonate solution and finally water. The ethereal solution was dried over magnesium sulfate, filtered, concentrated, and the residue was distilled, b.p. *ca.* 135° (0.3 mm.), $n^{26}D$ 1.4944, yield 0.13 g. (9%); ν_{max}^{film} 2930 and 2860 (C–H), 1743 (acetate C=O), 1645 (amide C=O) and 1235 cm.$^{-1}$ (acetate C–O). Hydroxyl absorption was absent.

Anal. Calcd. for $C_{12}H_{19}NO_3$: C, 63.97; H, 8.50; N, 6.22. Found: C, 63.74; H, 8.60; N, 5.83.

Sodium–Butanol Reduction of the Mixed 3-Acetoxyethyl- and 3-Hydroxyethyl-2-keto-3-azabicyclo[3.3.1]nonanes. 3-Hydroxyethyl-2-keto-3-azabicyclo[3.3.1]nonane (X).—To a solution of 5.27 g. of the mixed amido-alcohol and acetate in 50 ml. of butanol was added 5.3 g. of sodium. The mixture was heated under reflux for 2 hours, and 25 ml. of butanol was added to destroy the remaining sodium. After 2 more hours at reflux temperature, the mixture was steam distilled. The distillate was treated with concentrated hydrochloric acid and evaporated to dryness under reduced pressure to remove the butanol. The brown solid residue was taken up in water and the base was freed by addition of potassium carbonate and extraction with ether. Addition of methanolic picric acid to the extracts until they were just acid to congo red caused the separation of 1.92 g. (19%) of a picrate, m.p. 159–163°, which proved to be identical (mixture melting point) with the picrate of 3-hydroxyethyl-3-azabicyclo[3.3.1]nonane prepared earlier.

The residue from the steam distillation was extracted with chloroform. The extracts were given a preliminary drying with magnesium sulfate, filtered, concentrated and distilled through the Holzman column to give 2.62 g. (50% recovery) of oil, b.p. 136–142° (0.15 mm.), $n^{25}D$ 1.5178–1.5106. The infrared spectrum of the center cut, $n^{25}D$ 1.5140, indicated that the acetate had been completely removed; ν_{max}^{film} 3400 (O–H), 2930 and 2860 (C–H) and 1625 cm.$^{-1}$ (amide C=O), consistent with the structural assignment 3-hydroxyethyl-2-keto-3-azabicyclo[3.3.1]nonane.

Anal. Calcd. for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.52; H, 9.69; N, 7.40.

Mercuric Acetate Oxidation (25°) of 3-Hydroxyethyl-3-azabicyclo[3.3.1]nonane. 6-Aza-3-oxatricyclo[6.3.1.0^{2,6}]-dodecane (III).—To a solution of 122 g. of mercuric acetate in 320 ml. of 5% acetic acid was added 10.7 g. (0.064 mole) of 3-hydroxyethyl-3-azabicyclo[3.3.1]nonane. The mixture was stirred for 4.5 hours before the mercurous acetate was collected by filtration (33.3 g., 101% of theoretical for two-electron oxidation). The filtrate was saturated with hydrogen sulfide, and the mercury sulfides were removed with the aid of Filter-Cel. The filtrates were resaturated with hydrogen sulfide, and a slight additional amount of mercury sulfides was removed by filtration. The filtrate was made basic with potassium carbonate and extracted with ether. The base was recovered from the ether extracts in the usual way and distilled through the Holzman column to give 6.7 g. (62%) of the colorless oxazolidine, b.p. 111–114.5° (12 mm.), $n^{25}D$ 1.5032–1.5042. A center cut was redistilled to provide the samples for analysis and determination of the infrared spectrum, $n^{26}D$ 1.5040. The infrared spectrum (film) showed only one absorption band above 1500 cm.$^{-1}$, at 2940–2880 cm.$^{-1}$ (C–H). A sample of this compound was subjected to vapor phase chromatography. A single peak appeared, indicating that the material was homogeneous.

Anal. Calcd. for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.38. Found: C, 71.80; H, 10.37; N, 8.49.

The tricyclic oxazolidine was found[58] to have the following pK'_a values in the solvents indicated: 8.35 ± 0.03 (66% DMF), 9.03 ± 0.04 (33% DMF), 9.45 ± 0.05 (water). These represent the values in titrations from both the basic and acidic sides. The infrared spectrum of the tricyclic oxazolidine was determined[58] in acidic solution (DCl) in deuterium oxide as the solvent, using a calcium fluoride cell. A strong band appeared at 1682 cm.$^{-1}$, indicating that the salt (at least a portion of it) is in the ternary iminium form in aqueous solution.

The picrate was made by adding a solution of picric acid in methanol to the tricyclic oxazolidine in ether until the mixture was acid to congo red. The picrate crystallized as yellow hexagonal plates from ethanol, m.p. 174.5–175.2°. ν_{max}^{Nujol} 3340 (O–H) and 1685 cm.$^{-1}$ (>C=N$^+$<).

Anal. Calcd. for $C_{16}H_{20}N_4O_8$: C, 48.48; H, 5.09; N, 14.14. Found: C, 48.77; H, 5.10; N, 14.20.

Deuterium Exchange Studies with 6-Aza-3-oxatricyclo-[6.3.1.0^{2,6}]dodecane.—Deuteriomethanol (CH_3OD) was prepared by dissolving 23.0 g. of sodium metal in 250 ml. of methanol which had been freshly dried with magnesium methoxide. The methanol was removed under aspirator pressure, and the resulting solid was dried under high vacuum while heating on the steam-bath and rotating constantly. After two hours, methanol stopped accumulating in the Dry Ice trap, and the solid was a free-flowing powder. A certain amount of sodium methoxide dust was carried over into the Dry Ice trap in spite of the use of a glass wool plug in the top of the flask which was being evacuated. Heavy water (11.7 g., 99.7% D) was added, and the gummy mass was heated on the steam-bath for three hours. High vacuum was applied, and the methanol-*d* was collected in the Dry Ice trap. The product was redistilled, b.p. 65.1–66.1°, yield 24.1 g. (68% from heavy water). The infrared spectrum (5% solution in carbon tetrachloride) indicated that the ratio of O–D to O–H was approximately 70:30. The most likely reason for the presence of the hydrogen in this preparation was incomplete removal of the ordinary methanol from the powdery sodium methoxide.

A solution of 1.0 ml. of the tricyclic oxazolidine in about 5 ml. of deuteriomethanol was boiled under reflux for 27 hours. The liquid was then distilled through the Holzman column. The spectrum (film) of the center cut indicated the complete absence of C–D bonds in the material and was identical with that of the starting material.

To a solution of about 1 cu. mm. of sodium metal in 5 ml. of deuteriomethanol was added about 1 g. of the tricyclic oxazolidine. After a period of 3.5 hours of boiling under reflux, the mixture was distilled under reduced pressure through the Holzman column. The infrared spectrum (film) of a center cut had a very slight absorption at 2180 cm.$^{-1}$ but was otherwise the same as starting material. The weak absorption peak indicated that less than 5% of one hydrogen atom had exchanged.

A mixture of 1.27 g. of the tricyclic oxazolidine, 1.2 ml. of *pure* deuterium oxide and 6.8 ml. of sodium-dried dioxane was boiled under reflux for 24 hours. The mixture was fractionally distilled, and the high boiling fraction was redistilled with dry benzene. The tricyclic oxazolidine, b.p. 121.5–122° (16–19 mm.), $n^{25}D$ 1.5032, had an infrared spectrum (film) which showed significant, but still weak absorption at 2120 cm.$^{-1}$ (C–D). The deuterium analysis showed that exchange had occurred to less than 30% of one hydrogen exchanged.

Anal. Calcd. for $C_{10}H_{16}DNO$: atom % D, 5.88. Found: atom % D, 1.74.

Resolution of 6-Aza-3-oxatricyclo[6.3.1.0^{2,6}]dodecane.—To a solution of 2.30 g. (13.8 mmoles) of the tricyclic oxazolidine in 10 ml. of methanol was added 5.18 g. (13.8 mmoles) of dibenzoyl-*d*-tartaric acid monohydrate in 20 ml. of methanol. After 20 hours at 20°, 3.44 g. of salt was collected. This material was recrystallized once from a minimum of methanol as colorless needles, m.p. 161–163° dec., ν_{max}^{Nujol} 1680 cm.$^{-1}$ (>C=N$^+$<).

The salt was dissolved in cold aqueous potassium carbonate solution and extracted with four 10-ml. portions of chloroform. The base was recovered from the chloroform

(58) We wish to thank Dr. Harold Boaz, Eli Lilly and Co., Indianapolis, Ind., for his interest and for making these data available to us.

in the usual manner and was distilled at 60.3–61.0° (0.6 mm.), $n^{25}D$ 1.5037. The distilled base (0.32 g.) was dissolved in 5 ml. of ethanol, and the solution was poured into a jacketed 1-dm. polarimeter tube, $[\alpha]^{25}D$ −52.0 ± 0.7°.

Loss of Optical Activity of (−)-6-Aza-3-oxatricyclo[6.3.1.0^{2,6}]dodecane.—The ethanolic solution of the active base in the polarimeter tube was held at 65 ± 1° by means of a pump recirculating water through the jacket of the tube from a thermostated water-bath. The initial rotation (a) at 65° was −3.11 ± 0.03°. The rotation was followed for 48 hours. Activity was lost in a linear fashion, within experimental error, at a rate of 0.92 ± 0.05° (Δa) each 24 hours.

The 4-Methyldehydroquinolizidine System. Stability of 4-Methyl-Δ^4-dehydroquinolizidinium Perchlorate.—4-Methyl-Δ^4-dehydroquinolizidinium perchlorate,[53] m.p. 175–176°, was recovered essentially unchanged after subjection to the conditions: (a) boiling water for 24 hours, (b) acetic anhydride at 25° for 2 days and then heating at reflux for 5 minutes, (c) 2 hours at reflux in glacial acetic acid and (d) recrystallization from ethanol.

The 3-Methylhexahydropyrrocoline System. Mercuric Acetate Dehydrogenation of 3-Methyloctahydropyrrocoline.—3-Methyloctahydropyrrocoline[59] was dehydrogenated with mercuric acetate in the usual manner.[60] From 0.70 g. (5 mmoles) of the saturated base, there was obtained 0.50 g. (44%) of pure **3-methyl-Δ$^{4(9)}$-hexahydropyrrocolinium perchlorate**, m.p. 227–228° dec., ν_{max}^{Nujol} 1684 cm.$^{-1}$ (>C=N$^+$<).

Anal. Calcd. for $C_9H_{16}ClNO_4$: C, 45.48; H, 6.79; N, 5.89. Found: C, 45.74; H, 7.00; N, 5.83.

The base was liberated from a portion of the perchlorate and converted to **3-methyl-Δ$^{4(9)}$-hexahydropyrrocolinium picrate**, orange-yellow needles from ethanol, m.p. 132.5–135.5°.

Anal. Calcd. for $C_{15}H_{18}N_4O_7$: C, 49.18; H, 4.95. Found: C, 49.19; H, 5.00.

3-Methyl-Δ^2-hexahydropyrrocoline.—To the Grignard reagent prepared from 4.86 g. (0.20 g. atom) of magnesium and 28.4 g. (0.20 mole) of methyl iodide in 350 ml. of ether was added 13.9 g. (0.10 mole) of 3-ketoöctahydropyrrocoline[61,62] in 100 ml. of ether. The mixture was heated under reflux for 2 hours, and the excess Grignard reagent was destroyed with 130 ml. of 25% aqueous sulfuric acid. Basification with potassium carbonate and potassium hydroxide solutions was followed by ether extraction. The dried extracts were distilled giving two main fractions: (a) b.p. 56–70° (2.8 mm.), 4.0 g.; (b) 97–101° (2.6 mm.), 4.3 g. The second fraction was mainly 3-ketoöctahydropyrrocoline, as shown by comparison of its infrared spectrum with that of an authentic sample. The first fraction was treated with dilute perchloric acid in ethanol–ether, added in small portions, yielding two distinct perchlorate salts. The lower-melting salt was recrystallized from methanol–ethyl acetate, colorless needles, m.p. 151–152°, ν_{max}^{Nujol} 1682 cm.$^{-1}$ (>C=N$^+$<). The analysis agreed with the structural assignment as **3-methyl-Δ^3-hexahydropyrrocolinium perchlorate**. The compound was recovered unchanged after refluxing for 1 hour in glacial acetic acid.

Anal. Calcd. for $C_9H_{16}ClNO_4$: C, 45.48; H, 6.79; N, 5.89. Found: C, 45.50; H, 6.71; N, 5.82.

3-Methyl-Δ^2-hexahydropyrrocoline was generated from the perchlorate salt, b.p. 87.5° (22 mm.), ν_{max}^{film} 1643 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{15}N$: C, 78.77; H, 11.02. Found: C, 78.78; H, 11.17.

3-Methyl-Δ^3-hexahydropyrrocolinium picrate was formed in ether and was recrystallized from ethanol, orange needles, m.p. 158.5–159.5°.

Anal. Calcd. for $C_{15}H_{18}N_4O_7$: C, 49.18; H, 4.95; N, 15.30. Found: C, 49.23; H, 4.83; N, 15.07.

3,3-Dimethyloctahydropyrrocoline perchlorate was obtained as the higher-melting salt from the reaction of methylmagnesium iodide with 3-ketoöctahydropyrrocoline. Recrystallization from methanol–ethyl acetate yielded colorless plates, m.p. 249–250°, ν_{max}^{Nujol} 3090 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{20}ClNO_4$: C, 47.33; H, 7.95; N, 5.52. Found: C, 47.36; H, 7.80; N, 5.25.

2,3-Tetramethylene-2-oxazolinium Perchlorate (XIII).—Ring closure of 1-hydroxyethyl-2-piperidone (XIV)[63] was effected by heating it in ethanol solution for 1 hour with an equimolar amount of perchloric acid (64% in water).[64] When the reaction was run on a half-mole scale, the yield of 2,3-tetramethylene-2-oxazolinium perchlorate was 68%, colorless plates, m.p. 113–114°; ν_{max}^{Nujol} 1691 (>C=N$^+$<), 1267 (—O—C=) and 1090 cm.$^{-1}$ (ClO_4^-); no absorption maximum in the ultraviolet range (above 220 mμ).

Anal. Calcd. for $C_7H_{12}ClNO_5$: C, 37.26; H, 5.36; N, 6.21. Found: C, 37.45; H, 5.41; N, 6.12.

Reactions of 2,3-Tetramethylene-2-oxazolinium Perchlorate.—A solution of 2.26 g. (10 mmoles) of 2,3-tetramethylene-2-oxazolinium perchlorate and 16.3 g. of sodium acetate trihydrate in 47 ml. of 5% aqueous acetic acid was heated on the steam-bath for 4 hours. The mixture was cooled and extracted with seven 15-ml. portions of chloroform. The removal of chloroform was followed by distillation, b.p. 106–126° (0.2 mm.), yield 1.29 g. of a mixture of **1-acetoxyethyl-(XV) and 1-hydroxyethyl-2-piperidone (XIV)**; ν_{max}^{film} *ca.* 3380 (O–H), 2940, 2860 (C–H), 1745 (acetate C=O), 1650(sh), 1625 (amide C=O) and 1244 cm.$^{-1}$ (acetate C–O).

A mixture of 2.26 g. (10 mmoles) of 2,3-tetramethylene-2-oxazolinium perchlorate and 0.9 g. of anhydrous sodium acetate in 30 ml. of glacial acetic acid was heated at reflux for 3 hours. Acetic acid was removed at atmospheric pressure, and the product (0.94 g.) was collected by distillation under high vacuum, b.p. 101–102° (0.05 mm.), $n^{25}D$ 1.4734. The infrared maxima, similar to those listed above, and the elemental analysis were indicative of a mixture of **1-acetoxyethyl-** and **1-hydroxyethyl-2-piperidone**, with the former strongly predominating.

Anal. Calcd. for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Calcd. for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.66; H, 8.53; N, 7.75.

A mixture of 1.0 g. (4.4 mmoles) of 2,3-tetramethylene-2-oxazolinium perchlorate and 0.37 g. (4.4 mmoles) of potassium formate in 10 ml. of absolute ethanol was stirred under nitrogen for 8 hours, filtered, and the solid was washed with ethanol. The filtrate was concentrated and distilled, b.p. 150–152° (4.3–4.5 mm.), weight 0.37 g. The infrared spectrum indicated that the product was a mixture of **1-formoxyethyl-** and **1-hydroxyethyl-2-piperidone**, with the former strongly predominating; ν_{max}^{film} *ca.* 3350 (O–H), 2940, 2860 (C–H), 1725 (formate C=O), 1640 (amide C=O) and 1185–1170 cm.$^{-1}$ (formate C–O).

Reductions of 2,3-tetramethylene-2-oxazolinium perchlorate with sodium borohydride, sodium trimethoxyborohydride and hydrogen with platinum yielded mainly 1-hydroxylpiperidine.[65,66]

Preparation of 1-Hydroxyethyl-5-methyl-Δ^2-tetrahydropyridine. 1-Hydroxyethyl-5-methyl-2-pyridone.[67]—A mixture of 10.8 g. (0.10 mole) of redistilled 2-amino-5-methylpyridine and 8.05 g. (0.10 mole) of 2-chloroethanol was heated under nitrogen at 110° for 4 hours. The adduct was hydrolyzed by boiling for 16 hours with a solution of 22.4 g. (0.4 mole) of potassium hydroxide in 80 ml. of water. Extraction of the resulting solution with chloroform, and then solvent removal and distillation, yielded 6.0 g. (39%) of the pyridone, b.p. 150–153° (0.4 mm.), m.p. 85–86°, colorless needles from acetone–hexane.

Anal. Calcd. for $C_8H_{11}NO_2$: C, 62.72; H, 7.24; N, 9.14. Found: C, 62.96; H, 7.07; N, 9.27.

The phenylurethan was prepared by heating equimolar portions of the pyridone and phenyl isocyanate, m.p. 135–136°, colorless prisms from ethyl acetate.

Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.19; H, 5.69; N, 10.27.

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1-Hydroxyethyl-5-methyl-2-piperidone.—Hydrogenation of 1-hydroxyethyl-5-methyl-2-pyridone in glacial acetic acid with platinum yielded 93% of the corresponding piperidone, b.p. 125° (0.8 mm.); solidified on standing, m.p. 60–62.5°.

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.09; H, 9.60; N, 8.92.

Lithium Aluminum Hydride Reduction of 1-Hydroxyethyl-5-methyl-2-piperidone.[68,69]—A solution of 0.50 g. (0.013 mole) of lithium aluminum hydride in 100 ml. of ether was added dropwise to a stirred solution of 3.3 g. (0.021 mole) of the piperidone in 150 ml. of ether. After stirring and heating the mixture for 1 hour, sufficient saturated aqueous potassium carbonate solution was added to form a flocculent precipitate. The ether layer was decanted and distilled, giving a monomeric unsaturated hydroxyamine, b.p. 82–83° (23 mm.), $n^{20}D$ 1.4835, yield 0.633 g. (24%); ν_{max}^{film} *ca.* 3400 (O–H), 1660 cm.$^{-1}$ (C=C) (not analyzed). About 2.0 g. of the original piperidone was recovered.

Preparation of 2-Methyl-6-aza-9-oxabicyclo[4.3.0]nonane (XXII).—1-Hydroxyethyl-3-methyl-2-pyridone was obtained in 49% yield from 2-amino-3-methylpyridine by following directions similar to those described above for the position isomer, b.p. 119–122° (0.35 mm.), m.p. 85.5–86.5°, colorless needles from acetone–hexane.

Anal. Calcd. for $C_8H_{11}NO_2$: C, 62.72; H, 7.24; N, 9.14. Found: C, 62.96; H, 7.37; N, 9.07.

The phenylurethan crystallized as colorless prisms from ethyl acetate, m.p. 132.5–133.5°.

Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.09; H, 5.79; N, 10.19.

1-Hydroxyethyl-3-methyl-2-piperidone (XXII).—Catalytic hydrogenation of 1-hydroxyethyl-3-methyl-2-pyridone yielded 97% of the piperidone, b.p. 124° (1.3 mm.), $n^{23}D$ 1.4917.

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.12; H, 9.62. Found: C, 60.95; H, 9.53.

2,3-(α-Methyltetramethylene)-2-oxazolinium Perchlorate.—Ring closure of 1-hydroxyethyl-3-methyl-2-piperidone was effected by boiling in ethanol solution with an equivalent amount of perchloric acid (70% in water), yielding 2,3-(α-methyltetramethylene)-2-oxazolinium perchlorate, m.p. 123–124°, colorless plates from ethanol–ethyl acetate, ν_{max}^{Nujol} 1683 cm.$^{-1}$ (>C=N$^+$<).

Anal. Calcd. for $C_8H_{14}ClNO_5$: C, 40.09; H, 5.89; N, 5.85. Found: C, 39.96; H, 5.80; N, 5.73.

Sodium and Butanol Reduction of 1-Hydroxyethyl-3-methyl-2-piperidone (XXI).—The reduction was carried out according to the directions of Lukeš and Kovář,[70] which had been used previously for the reduction of 1,3-dimethyl-2-piperidone.[71] The major product was a colorless oil, b.p. 86.5–90° (23–25 mm.), $n^{25}D$ 1.4673, which was assigned the structure **2-methyl-6-aza-9-oxabicyclo[4.3.0]nonane (XXII)** (66% yield) on the basis of elemental analysis and infrared maxima characteristic of oxazolidines[72,73] (1085, 1182 cm.$^{-1}$; very weak absorption was also observed in the 3 and 6 μ regions, probably indicative of the presence of a slight amount of 1-hydroxyethyl-3-methyl-Δ^2-tetrahydropyridine).

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 67.83; H, 10.74; N, 9.96.

The picrate crystallized from ethanol as yellow needles, m.p. 94–95°.

Anal. Calcd. for $C_{14}H_{18}N_4O_8$: C, 45.40; H, 4.90. Found: C, 45.75; H, 4.95.

Deuterium Exchange Studies with 2-Methyl-6-aza-9-oxabicyclo[4.3.0]nonane (XXII).—A mixture of 0.66 g. of redistilled oxazolidine and 2.0 ml. of deuteriomethanol was heated under reflux for 2 hours and then distilled under reduced pressure. The infrared spectrum of a center cut (film) showed that less than 5% of one hydrogen had exchanged (very weak absorption at 2160 cm.$^{-1}$ (C–D)).

A mixture of 1.22 g. of the oxazolidine, 1.6 ml. of pure deuterium oxide and 8 ml. of sodium-dried dioxane was heated under reflux for 23 hours. Dry benzene was added, and the mixture was distilled under reduced pressure. The infrared spectrum of a center cut indicated that the sample was still wet, but the fact that only about 5% of one hydrogen had exchanged was evident from the weak absorption at 2150 cm.$^{-1}$ (C–D).

1-Hydroxyethyl-3,3-dimethylpiperidine.—A solution of 11.3 g. (0.10 mole) of 3,3-dimethylpiperidine[74a] and 8.0 g. (0.1 mole) of 2-chloroethanol in 50 ml. of toluene was maintained at the reflux temperature for 11 hours. The hydrochloride salt was collected by filtration and converted to the base, b.p. 105–107° (21 mm.), $n^{25}D$ 1.4623.[74b]

Anal. Calcd. for $C_9H_{19}NO$: C, 68.74; H, 12.18; N, 8.91. Found: C, 68.61; H, 12.15; N, 9.02.

The picrate crystallized from ethanol as yellow prisms, m.p. 126.5–127.5°.

Anal. Calcd. for $C_{15}H_{22}N_4O_8$: C, 46.63; H, 5.74; N, 14.50. Found: C, 46.66; H, 5.65; N, 14.33.

Mercuric Acetate Oxidation of 1-Hydroxyethyl-3,3-dimethylpiperidine.—Treatment of 5.0 g. (0.032 mole) of 1-hydroxyethyl-3,3-dimethylpiperidine with 40.5 g. (0.127 mole) of mercuric acetate in the usual manner[27] gave low- and high-boiling products. The high-boiling product was obtainable also by extraction of the aqueous acid solution with methylene chloride (after precipitation of mercuric sulfide) and was therefore more nearly neutral. The low-boiling basic oil, b.p. 89–91° (21 mm.), weighed 2.33 g. and was considered, on the basis of the infrared absorption maxima (liquid film) at 3415 (O–H) and 1663 cm.$^{-1}$ (C=C), to be mainly **1-hydroxyethyl-5,5-dimethyl-Δ^2-tetrahydropyridine**, although the possible presence of the isomeric 2,2-dimethyl-6-aza-9-oxabicyclo[4.3.0]nonane and 4,4-dimethyl-6-aza-9-oxabicyclo[4.3.0]nonane cannot be disregarded.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.63; H, 11.04. Found: C, 68.97; H, 11.10.

The picrate crystallized as yellow plates from ethanol, m.p. 120–121°.

Anal. Calcd. for $C_{15}H_{20}N_4O_8$: C, 46.87; H, 5.25; N, 14.58. Found: C, 46.98; H, 5.44; N, 14.49.

The weight of the high-boiling product was 1.63 g., b.p. 151° (0.6 mm.). The elemental analysis, the infrared spectrum (ν_{max}^{film} 3390 (O–H), 1738 (ester C=O), *ca.* 1622 cm.$^{-1}$ (lactam C=O)) and our previous experience with the conversions of the 2,3-tetramethylene-2-oxazolinium salt in the presence of acetic acid and acetate ion (see above) combined to indicate that this product was mainly **1-acetoxyethyl-3,3-dimethyl-2-piperidone** ($C_{11}H_{19}NO_3$), possibly contaminated with 1-hydroxyethyl-3,3-dimethyl-2-piperidone ($C_9H_{17}NO_2$) (see below).

Anal. Calcd. for $C_{11}H_{19}NO_3$: C, 61.94; H, 8.98; N, 6.57. Found: C, 61.83; H, 9.22; N, 6.81.

2,3-(α,α-Dimethyltetramethylene)-2-oxazolinium perchlorate was made by boiling a solution of 0.57 g. of the product having an analytical composition close to $C_{11}H_{19}NO_3$ with 0.51 g. of 70% perchloric acid in 3 ml. of ethanol for 15 minutes. About 0.5 g. of colorless needles separated on cooling and, after repeated recrystallization from ethanol, the melting point was 211–214°, ν_{max}^{Nujol} 1672 cm.$^{-1}$ (>C=N$^+$<).

Anal. Calcd. for $C_9H_{16}ClNO_5$: C, 42.61; H, 6.36; N, 5.52. Found: C, 43.08; H, 6.37; N, 5.45.

Reduction with sodium borohydride gave 1-hydroxyethyl-3,3-dimethylpiperidine, identified as the picrate.

1-Hydroxyethyl-3,3-dimethyl-2-piperidone was obtained by dissolving the perchlorate salt in water, basifying with sodium hydroxide pellets, extracting with ether and distilling, b.p. 114° (0.3 mm.), ν_{max}^{film} 3390 (O–H) and 1621 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{17}NO_2$: C, 63.13; H, 10.00; N, 8.18. Found: C, 63.45; H, 10.17; N, 8.13.

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The Arylaralkyloxazolidine System. 2-Phenyl-3-(*p*-methoxybenzyl)-oxazolidine (XXIII).—A solution of 24.5 g. (0.135 mole) of 2-(*p*-methoxybenzylamino)-ethanol[75,76] and 14.33 g. (0.135 mole) of benzaldehyde in 100 ml. of benzene was heated at reflux for 25 minutes in a Dean–Stark apparatus. The residue after removal of the benzene was distilled at 168° (0.45 mm.) to give 29 g. (80%) of 2-phenyl-3-(*p*-methoxybenzylamino)-oxazolidine, $n^{21.5}$D 1.5707. The infrared spectrum (carbon tetrachloride) showed no absorption in the O–H stretching region and exhibited maxima characteristic of oxazolidines[72,73] at 1168, 1057, 1041 and 1025 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.74; H, 7.14; N, 5.46.

Hydrolysis.—Three grams of 2-phenyl-3-(*p*-methoxybenzyl)-oxazolidine was hydrolyzed by shaking with 3.0 ml. of 6 *N* hydrochloric acid. Removal of the neutral material by methylene chloride extraction was followed by basification with potassium hydroxide. Extraction with methylene chloride followed by drying and evaporation gave 1.57 g. (90%) of pure 2-(*p*-methoxybenzylamino)-ethanol (infrared spectrum virtually identical with that of an authentic sample).

Isomerization Experiments.—(a) A solution of 3.0 g. of 2-phenyl-3-(*p*-methoxybenzyl)-oxazolidine in 75 ml. of absolute methanol was heated at reflux for 24 hours. Evaporation of the methanol *in vacuo* was followed by the hydrolysis procedure above. 2-(*p*-Methoxybenzylamino)-ethanol was obtained in 99% yield (2.01 g.), with an infrared spectrum virtually identical with that of an authentic sample.

(b) A solution of 3.0 g. of 2-phenyl-3-(*p*-methoxybenzyl)-oxazolidine in 15 ml. of diethylene glycol monomethyl ether was heated at reflux under nitrogen for 24 hours. Upon hydrolysis, there was obtained 1.80 g. of basic material. The infrared spectrum of this material indicated that it was a mixture of 2-(*p*-methoxybenzylamino)-ethanol and 2-(benzylamino)-ethanol, in roughly equal amounts.

2-(*p*-Methoxyphenyl)-3-benzyloxazolidine (XXIV).—A solution of 25 g. (0.165 mole) of 2-(benzylamino)-ethanol[77] and 22.5 g. (0.165 mole) of anisaldehyde in 100 ml. of benzene was heated at reflux for 25 minutes in a Dean–Stark apparatus. The residue after removal of the benzene was distilled at 161–164° (0.35 mm.) to give 28.5 g. (64%) of 2-(*p*-methoxyphenyl)-3-benzyloxazolidine, $n^{21.5}$D 1.5717. The infrared spectrum (carbon tetrachloride) showed no absorption attributable to O–H stretching and exhibited bands characteristic of oxazolidines[72,73] at 1171, 1065 and 1043 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.53; H, 7.05; N, 5.06.

Hydrolysis.—Cleavage of 2-(*p*-methoxyphenyl)-3-benzyloxazolidine as described for the isomer gave pure 2-(benzylamino)-ethanol in 97% yield (1.96 g.), as shown by its infrared spectrum.

Isomerization Experiments.—(a) Treatment of 3.0 g. 2-(*p*-methoxyphenyl)-3-benzyloxazolidine in 75 ml. of refluxing methanol for 24 hours yielded 98% (1.66 g.) of 2-(benzylamino)-ethanol, as shown by its infrared spectrum.

(b) Repetition of the diethylene glycol monomethyl ether experiment on this isomer gave 1.81 g. of basic material which had an infrared spectrum indicative of a mixture of the two ethanolamines.

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URBANA, ILL.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, GEORGIA INSTITUTE OF TECHNOLOGY]

The Reductive Cyclization of Indolylethylisoquinolinium Salts[1]

BY JOHN W. HUFFMAN

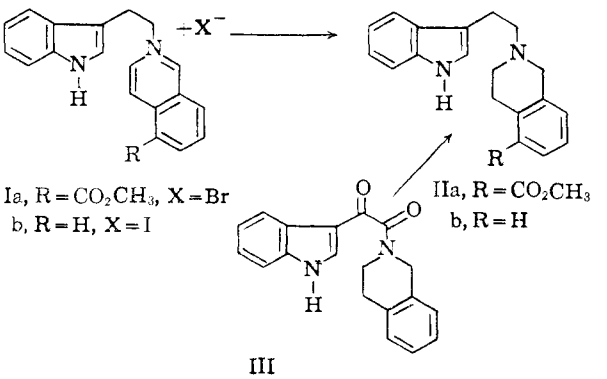
RECEIVED MAY 1, 1958

Sodium borohydride reduction of 2-[2-(3-indolyl)-ethyl]-isoquinolinium salts has been shown to yield the corresponding 1,2,3,4-tetrahydroisoquinoline. Lithium aluminum hydride reduction, however, yields the 1,2-dihydroisoquinoline, which undergoes extremely facile ring closure to 5,7,8,13,13b,14-hexahydrobenzo[g]indolo[2,3a]quinolizine.

The great deal of attention which has been focused on the reductive cyclization of various 2-[2-(3-indolyl)-ethyl]-isoquinolinium salts,[2–4] and in particular the failures reported when sodium borohydride is used as a reducing agent prompted us to undertake a study of the mechanism of this interesting reaction. This reaction recently has taken on even greater significance with its use in the synthesis of alstonilol.[5]

We first turned our attention toward the nature of the sodium borohydride reduction of these systems. It has been reported[4] that 2-[2-(3-indolyl)-ethyl]-5-carbomethoxyisoquinolinium bromide (Ia) on reduction with sodium borohydride gave a material isomeric with, but not identical to, tetrahydroalstoniline, and also that reduction of Ib with potassium borohydride gives largely unidentified material.[2]

In our hands, reduction of 2-[2-(3-indolyl)-ethyl]-isoquinolinium iodide (Ib) with sodium borohydride afforded a compound $C_{19}H_{20}N_2$. The



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picrate of this material had a melting point which corresponded to that reported for 2-[2-(3-indolyl)-ethyl]-1,2,3,4-tetrahydroisoquinoline.[2]

An authentic sample of the tetrahydroisoquino-

(1) Presented at the 35th Annual Meeting of the Georgia Academy of Sciences, Emory University, April 25, 1958.

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