zation from methanol (15 cc.) raised the melting point to 128–129°. This compound did not depress the melting point of 1-(β-methylaminoethyl)-3-nitro-2-imidazolidone nitrate (m.p. 128–129°) prepared as described above in method A.

Reaction of 1-(β-Chloroethyl)-2-imidazolidone with Methanolic Potassium Hydroxide Solution.—Methanolic potassium hydroxide solution (59 cc. of 1.7 *N* solution) was added dropwise over a period of 40 minutes to a stirred solution of 1-(β-chloroethyl)-2-imidazolidone (14.8 g., 0.1 mole) in methanol (50 cc.). This solution, which was refluxing during the addition period, was refluxed for a further period of 6 hr. After the solution cooled the potassium chloride was removed by filtration and the filtrate was taken to dryness *in vacuo* under nitrogen. The semi-crystalline residue was extracted with chloroform (60 cc.) which left behind a second crop of potassium chloride. The total yield of potassium chloride was 7.33 g. (98.3%). A colorless mobile oil (12.8 g.) was recovered from the chloroform extract on evaporation. This oil (b.p. 88–117° (0.13–0.17 mm.)) was a mixture of three products. A sample (251.7 mg.) of the oil on treatment with alcoholic picric acid solution in the usual manner gave a 21.7% yield of a crystalline picrate (m.p. 136–140°). Three crystallizations from acetone–ether raised the melting point of the Δ^7-1-oxa-4,7-diazabicyclo[3.3.0]octene picrate to 144.5–145.5°.

Anal. Calcd. for $C_{11}H_{11}N_5O_3$: C, 38.71; H, 3.25; N, 20.52. Found: C, 39.02; H, 3.51; N, 20.68.

A second run using 59.2 g. (0.4 mole) of 1-(β-chloroethyl)-2-imidazolidone gave 43.8 g. of a crude yellow oil. This oil on distillation *in vacuo* under nitrogen gave the following fractions: I, 5.32 g. of colorless crystals (b.p. 94–99° (0.25 mm.)); II, 3.98 g. of crystals and oil (b.p. 99–107° (0.14 mm.)); III, 7.76 g. of colorless liquid (b.p. 104–113° (0.13 mm.)); IV, 19.61 g. of colorless liquid which partly solidified (b.p. 115–120° (0.26–0.40 mm.)); V, 3.5 g. of crystals and oil (b.p. 119° (0.11 mm.)).

Picrates (m.p. 139–144°) were obtained in the usual manner from these fractions in 45.2, 29.1, 23.0, 8.29 and 2.95% yield, respectively. These purified picrates (m.p. 143–144°) did not depress the melting point of Δ^7-1-oxa-4,7-diazabicyclo[3.3.0]octene picrate (m.p. 144.5–145.5°).

Fractions II and III on analysis for 1-vinyl-2-imidazolidone by iodometric titration gave 20 and 47% unsaturation, respectively.

After fraction IV had remained at room temperature for two days, large crystals were deposited. These crystals were removed by filtration and then crystallized from acetone, yield 2.74 g. The melting point of 1-(β-methoxyethyl)-2-imidazolidone was raised from 61–68° to 67.5–68.5° by three crystallizations from acetone–petroleum ether (1:1) solution.

Anal. Calcd. for $C_6H_{12}N_2O_2$: C, 49.98; H, 8.39; N, 19.44. Found: C, 49.87; H, 8.32; N, 19.85.

Although these runs were repeated several times, pure samples of Δ^7-1-oxa-4,7-diazabicyclo[3.3.0]octene or 1-vinyl-2-imidazolidone have not been obtained at present.

Ammonolysis of Δ^7-1-Oxa-4,7-diazabicyclo[3.3.0]octene.—A sample of oil (1.06 g.) containing 21.7% of Δ^7-1-oxa-4,7-diazabicyclo[3.3.0]octene by picrate analysis mixed with 1-(β-methoxyethyl)-2-imidazolidone was dissolved in concentrated ammonia solution (25 cc.) and allowed to stand at room temperature for 16 hr. This solution on evaporation *in vacuo* under nitrogen gave 1.07 g. of viscous oil. The oily reaction product was dissolved in absolute ethanol (25 cc.) and dry hydrogen chloride was bubbled through the solution. A crystalline precipitate (m.p. 142–143°) was obtained in 61.4% (0.21 g.) yield. These crystals on admixture with 1-(β-hydroxyethyl)-2-iminoimidazolidine hydrochloride (m.p. 142.5–143°) gave no depression in melting point.

A picrate was prepared from the reaction product in the usual manner from water and it melted at 144.5–145°. This picrate did not depress the melting point of 1-(β-hydroxyethyl)-2-iminoimidazolidine picrate (144–145°), but it did depress the melting point of Δ^7-1-oxa-4,7-diazabicyclo-[3.3.0]octene picrate (m.p. 144.5–145.5°) to 131–136°.

A pure sample of 1-(β-methoxyethyl)-2-imidazolidone (m.p. 67.5–68.5°) treated with concentrated ammonia solution under the conditions described above was recovered unchanged in quantitative yield.

VILLE LASALLE, QUEBEC

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

Unsaturated Amines. X. The Mercuric Acetate Route to Substituted Piperidines, Δ^2-Tetrahydropyridines and Δ^2-Tetrahydroanabasines

BY NELSON J. LEONARD AND FRED P. HAUCK, JR.[1,2]

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The course of the mercuric acetate oxidation of tertiary amines has been studied intensively by employing a series of piperidines in which alkyl substitution on the ring has been varied systematically with respect to both position and degree. As a result of this study we are now in a position to predict with some degree of assurance the fate of a given substituted piperidine when subjected to mercuric acetate oxidation. Moreover, we have advanced our knowledge of the chemical reactivities and spectral properties of enamines and their related ternary iminium salts. Benefits to be derived from the present study in terms of synthesis include generally applicable methods for making substituted Δ^2-tetrahydropyridines and—through these as intermediates—piperidines having multiple substitution, together with a new useful method for the preparation of a series of Δ^2-tetrahydroanabasines.

In the process of gaining fundamental information concerning the dehydrogenating action of mercuric acetate on tertiary amines,[3] a reagent which has been employed in the modification of alkaloid structures,[4–6] we have investigated its action on model tetracyclic and bicyclic bases. The next important step to be taken was the examination of the transformations brought about by mercuric acetate on simple *monocyclic* tertiary amines. Several series of alkyl-substituted piperidines were selected for this study. As a result of the present investigation, we have accumulated sufficient knowledge to make relatively assured predictions

(1) National Science Foundation Fellow, 1953–1954.

(2) Sinclair Refining Co. Fellow in Organic Chemistry, 1954–1956. Work done under the sponsorship of the Sinclair Resaerch Laboratories, Inc.; see F. P. Hauck, Jr., Ph.D. Thesis, University of Illinois, 1956.

(3) For successive papers in this series, see: (a) N. J. Leonard and V. W. Gash, THIS JOURNAL, **76**, 2781 (1954); (b) N. J. Leonard and D. M. Locke, *ibid.*, **77**, 437 (1955); (c) N. J. Leonard, A. S. Hay, R. W. Fulmer and V. W. Gash, *ibid.*, **77**, 439 (1955); (d) N. J. Leonard, P. D. Thomas and V. W. Gash, *ibid.*, **77**, 1552 (1955); (e) N. J. Leonard and A. S. Hay, *ibid.*, **78**, 1984 (1956); (f) N. J. Leonard, W. J. Middleton, P. D. Thomas and D. Choudhury, *J. Org. Chem.*, **21**, 344 (1956); (g) N. J. Leonard, R. W. Fulmer and A. S. Hay, THIS JOURNAL, **78**, 3457 (1956); (h) N. J. Leonard, L. A. Miller and P. D. Thomas, *ibid.*, **78**, 3463 (1956); (i) N. J. Leonard and R. R. Sauers, *ibid.*, **79**, in press (1957).

(4) Reference 3c, footnote 5.

(5) F. L. Weisenborn and P. A. Diassi, THIS JOURNAL, **78**, 2022 (1956).

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

as to the course of the mercuric acetate oxidation of cyclic tertiary amines. Moreover, we have advanced our knowledge of the chemical reactivities and spectral properties of enamines (α,β-unsaturated amines) and their related ternary iminium salts ($>C{=}N^+ < X^-$). In addition, we have developed synthetic sequences which are generally applicable to the preparation of variously substituted piperidines, Δ^2-tetrahydropyridines and Δ^2-tetrahydroanabasines.

Enamine Detection

Since the most general action of mercuric acetate on cyclic tertiary amines is the introduction of α,β-unsaturation, it is presently desirable to collate the methods which can be used for enamine detection and to indicate briefly the known limitations in their application. These methods have direct bearing on the chemistry of the substituted piperidines and their oxidation products.

pK_a': α,β-Unsaturated tertiary amines are generally stronger bases than the corresponding saturated amines or β,γ-unsaturated amines.[3c,d,7]

Infrared: There is generally observed a decided shift toward higher frequency of the double bond stretching maximum in going from an α,β-unsaturated amine to the corresponding (ternary iminium) salt.[3a,8,9] When Cβ-protonation is prevented sterically, the infrared shift is not observed.[3a]

Ultraviolet: A definite shift toward longer wave length and higher intensity of absorption is observed with the introduction of unsaturation α,β to tert.-amino nitrogen.[3b,10] Application of this method has been limited to examples which contain no complicating chromophore.

Zerewitinoff: The absence of active hydrogen has been used in bolstering the assignment of ternary iminium salt structures (*vs.* N-protonated salt forms),[3c,h] but this method must be employed with caution, since the rate of nucleophilic attack of the Grignard anion at the α-carbon of the ternary iminium salt cannot be expected in all cases to exceed greatly the rate of abstraction of hydrogen from the β-carbon.[3d,f]

Grignard Addition: Related conversely to the active hydrogen determination is the isolation of Cα-substituted products from the reaction of organomagnesium and organolithium reagents with ternary iminium salts,[3c–e,11] an application of the early work of Freund and others with aromatic quaternary salts.[12] Not all ternary iminium salts necessarily react, however, with methylmagnesium iodide or methyllithium in this manner, as will be seen in the present investigation.

Metal Hydrides: Unsaturated tertiary amines are not reduced, but ternary iminium salts *are* reduced by lithium aluminum hydride and sodium borohydride.[13]

Potassium Cyanide: This compound reacts quickly and practically completely with ternary iminium salts in solution to give α-tert.-aminonitriles and accordingly serves as an excellent characterizing reagent and provides as well a versatile type of intermediate.[3d-h] The related reaction of cyanide ion with the conjugated $>C{=}N^+<$ function was investigated originally by Kaufmann and others.[14]

Clemmensen Reduction: The reducibility of enamines with zinc and acid, as the ternary iminium salts,[3d,5] is in contrast with the non-reducibility of amines possessing unsaturation further removed than the α_N-carbon.

Formic Acid: Reduction of an unsaturated amine with approximately one molar equivalent of formic acid proceeds readily when the unsaturation is α,β to the nitrogen[15,3d,h] and Cβ-protonation is not sterically prevented,[16,17] and reduction does not proceed when the double bond is β,γ or further removed from the nitrogen.[16] It is conceivable that the liberation of carbon dioxide could be used to indicate that a tertiary amine is α,β-unsaturated, provided the materials were pure and no other group in the substrate molecule was formic acid-reducible.

Synthesis of Substituted Piperidines

From a unified survey of the methods available for the detection of enamines and ternary iminium salts and for modifying their structures, we turn to the synthesis of the substituted piperidines which served as model precursors for the introduction of unsaturation by means of mercuric acetate. Several of the requisite amines were known already and have been prepared as indicated at the beginning of the Experimental section. Several substituted piperidines were prepared by the simple device of N-alkylation, as for 1,2-diethylpiperidine, 1,2-dimethyl-5-ethylpiperidine, 1,2,2,6,6-pentamethylpiperidine and 1,3,3-trimethylpiperidine, or N-alkylation concomitant with reduction, as for 1-ethyl-4-methylpiperidine. Wolff–Kishner reduction of 3,5-diethyl-1-methyl-4-piperidone[18] furnished 3,5-diethyl-1-methylpiperidine; a similar method was used for 2,6-diethyl-1-methylpiperidine, and 1,4,4-trimethylpiperidine was obtained by lithium aluminum hydride reduction of the corresponding N,β,β-trimethylglutarimide. The action of Grignard reagents on 2-piperidones[19–21] was used to pre-

(7) R. Adams and J. E. Mahan, THIS JOURNAL, **64**, 2588 (1942).

(8) B. Witkop and J. B. Patrick, *ibid.*, **75**, 4474 (1953).

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

(10) E. A. Braude, *Ann. Reps. Chem. Soc.*, **42**, 105 (1945); K. Bowden, E. A. Braude, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 45 (1946); K. Bowden, E. A. Braude and E. R. H. Jones, *ibid.*, 948 (1946); M. E. Herr and F. W. Heyl, THIS JOURNAL, **74**, 3627 (1952); F. W. Heyl and M. E. Herr, *ibid.*, **75**, 1918 (1953); J. L. Johnson, M. E. Herr, J. C. Babcock, A. E. Fonken, J. E. Stafford and F. W. Heyl, *ibid.*, **78**, 430 (1956).

(11) K. Wiesner, Z. Valenta, A. J. Manson and F. W. Stonner, *ibid.*, **77**, 675 (1955).

(12) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-metallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, pp. 1251–1255.

(13) Reference 3c, footnote 7, and N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, pp. 781 ff.

(14) Reference 3d, footnote 16.

(15) P. L. deBenneville and J. H. Macartney, THIS JOURNAL, **72**, 3073 (1950); P. L. deBenneville, U. S. Patent 2,578,787 (1951).

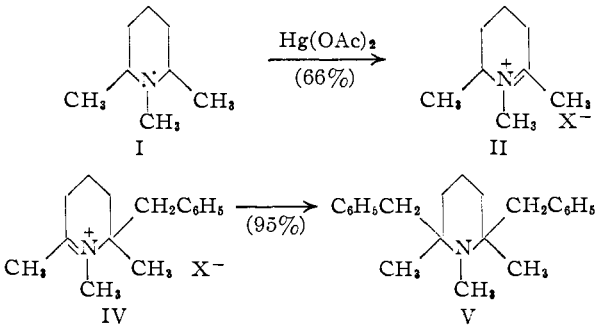
(16) N. J. Leonard and W. D. Smart, unpublished results.

(17) R. R. Sauers, Ph.D. Thesis, University of Illinois, 1956.

(18) C. Mannich and P. Schumann, *Ber.*, **69B**, 2299 (1936).

(19) (a) R. Lukeš, *Chem. Listy*, **22**, 1 (1928); (b) R. Lukeš and J. Malek, *ibid.*, **45**, 72 (1951); (c) R. Lukeš, *ibid.*, **46**, 726 (1952); (d) R. Lukeš and M. Smetackova, *Coll. Czech. Chem. Commun.*, **6**, 231 (1934); (e) R. Lukeš and K. Smolek, *ibid.*, **7**, 476 (1935); (f) R. Lukeš and J. Přeučil, *ibid.*, **7**, 482 (1935); (g) R. Lukeš and J. Gorocholinskij, *ibid.*, **8**, 223 (1936); (h) R. Lukeš and V. Šperling, *ibid.*

pare both saturated and unsaturated piperidines. For example, reaction of 1,3-dimethyl-2-piperidone with a threefold excess of ethylmagnesium iodide yielded 40% of 2,2-diethyl-1,3-dimethylpiperidine and 32% of 1,3-dimethyl-2-ethyl-Δ^2-tetrahydropyridine (isolated as 1,3-dimethyl-2-ethyl-Δ^1-tetrahydropyridinium perchlorate). The hydrogenation of a series of substituted Δ^1-tetrahydropyridinium perchlorates in ethanol using platinum oxide was very rapid and gave nearly quantitative yields of the correspondingly substituted piperidines. Combinations of Grignard reagents with substituted Δ^1-tetrahydropyridinium perchlorates were used to provide piperidines with additional substitution at the 2-position. Excellent results were obtained with benzylmagnesium chloride, variable results with ethylmagnesium iodide and poor results with methylmagnesium iodide. The synthetic application of alternating mercuric acetate oxidations and Grignard additions may be illustrated by the very effective preparation of 2,6-dibenzyl-1,2,6-trimethylpiperidine (V, stereochemistry not determined) starting with 1,2,6-trimethylpiperidine (I).

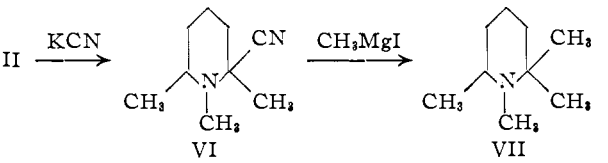


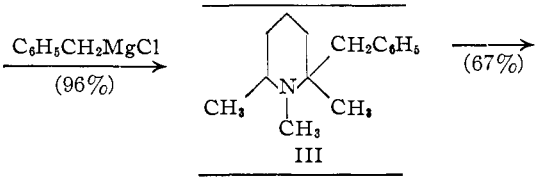
Numerous other examples will be found following the detailed discussion of the mercuric acetate oxidation of substituted piperidines.

Mercuric Acetate Oxidation of Substituted Piperidines

The previous work with mercuric acetate in this Laboratory and elsewhere on alkaloids and on bicyclic tertiary amine systems led us to expect a variety of products when this oxidizing agent was applied for the first time to monocyclic tertiary amines. We have now determined at least the major products formed in the mercuric acetate oxidation, in aqueous acetic acid solution, of substituted piperidines, in which the location and degree of alkyl substitution have been varied systematically. The nature of the products formed shows a marked dependence on both location and degree of substitution on the piperidine ring, and a number of interesting generalizations can be made as a result of the present study.

1-Methyl-2,6-dialkylpiperidines (I and 2,6-diethyl-1-methylpiperidine were the examples) are oxidized by mercuric acetate at one of the equivalent 2- and 6-positions. The position of the double bond in the unsaturated amine obtained from 1,2,6-trimethylpiperidine (I) was established as α,β to the nitrogen by comparison of the infrared frequency of the double bond stretching maximum[3a] for the base 1,2,6-trimethyl-Δ^2-tetrahydropyridine (1650 cm.$^{-1}$) with that for its salt II, 1,2,6-trimethyl-Δ^1-tetrahydropyridinium perchlorate (1679 cm.$^{-1}$), and by the efficient reaction of the salt II with aqueous potassium cyanide[3d] to give 2-cyano-1,2,6-trimethylpiperidine (VI). The position of the double bond in II was further confirmed by its reaction with benzylmagnesium chloride, mentioned above (II → III), and the related 2-location of the nitrile grouping in VI by its displacement with methyl,[3d,e] as in VI → VII. Similar methods





were used to establish the structures of other α,β-unsaturated amines encountered in this series.

1,2-Dialkylpiperidines (1,2-dimethyl-(VIIIa), 1,2-diethyl-(VIIIb) and 2-ethyl-1-methylpiperidine (VIIIc) were the examples) are oxidized by mercuric acetate preferentially at the tertiary α-carbon. From 1,2-dimethylpiperidine no basic product (1,6-dimethyl-Δ^2-tetrahydropyridine or its high-boiling self-condensation product) was isolated corresponding to oxidation at the secondary α-carbon.[22] A large-scale run resulted mainly in the production of 1,2-dimethyl-Δ^2-tetrahydropyridine, convertible to the ternary iminium salt IXa, 1,-2-dimethyl-Δ^1-tetrahydropyridinium perchlorate. This salt was converted in 97% yield to 2-cyano-1,2-dimethylpiperidine (Xa), which on lithium aluminum hydride reduction gave 1,2-dimethylpiperidine, a behavior indicative of an amino-α-tert.-nitrile in this series (see below) and therefore confirmation of the assigned structures X and IX. We had found previously that the tert.-nitrile grouping in the related 10-cyanoquinolizidine was replaced by hydrogen upon treatment with lithium aluminum hydride.[3e]

1-Methyl-2,5-dialkylpiperidines (XI) are oxidized by mercuric acetate preferentially at the tertiary α-carbon. The final step in the sequence XIc → XII → XIII → XIc established this in the case of 1,2-dimethyl-5-ethylpiperidine.

1-Methyl-2,3-dialkylpiperidines (XIV) are also oxidized by mercuric acetate preferentially at the tertiary α-carbon. Thus, the main basic product

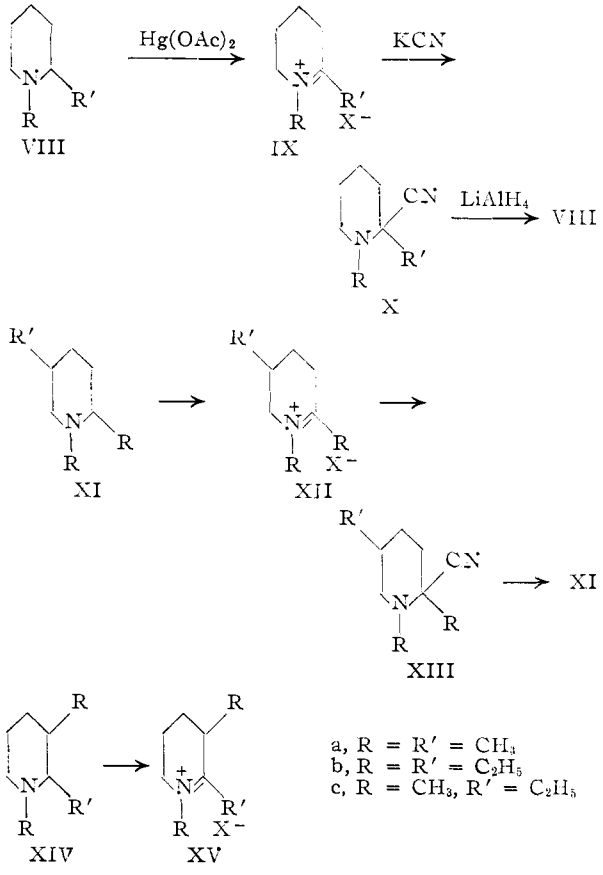
8, 461 (1936); (i) R. Lukeš and O. Grossmann, *ibid.*, **8**, 533 (1936); (j) R. Lukeš and K. Smolek, *ibid.*, **11**, 506 (1939); (k) R. Lukeš and F. Šorm, *ibid.*, **12**, 356 (1947); (l) R. Lukeš, F. Šorm and Z. Arnold, *ibid.*, **12**, 641 (1947); (m) R. Lukeš and J. Dobáš, *ibid.*, **15**, 303 (1950); (n) R. Lukeš and M. Večeřa, *ibid.*, **19**, 263 (1954).

(20) E. Ochiai, K. Tsuda and J. Yokoyama, *Ber.*, **68B**, 2291 (1935).

(21) J. Lee, A. Ziering, S. Heineman and L. Berger, *J. Org. Chem.*, **12**, 885 (1947).

(22) It must be admitted, however, that possible neutral products, such as 1,6-dimethyl-2-piperidone, might have escaped our attention in the initial stages of the investigation since we have concerned ourselves mainly with the nature of the basic products.

from 1,2,3-trimethylpiperidine (XIVa) was 1,2,3-trimethyl-Δ^2-tetrahydropyridine, identical with authentic material, isolated as the perchlorate salt XVa. 1,3-Dimethyl-2-ethylpiperidine (XIVc) yielded 1,3-dimethyl-2-ethyl-Δ^2-tetrahydropyridine after purification through the perchlorate salt XVc,



m.p. 237–238.5°. In addition, an appreciable amount of higher-boiling unsaturated, hydroxylated product was obtained, as indicated by the infrared spectrum (ν_{max}^{Nujol} 3440, 1672 cm.$^{-1}$) of a second perchlorate salt, m.p. 224–229° dec. The position of the hydroxyl group was not established, but the most logical formulation of this salt is 1,3-dimethyl-2-ethyl-3-hydroxy-Δ^1-tetrahydropyridinium perchlorate. Other tertiary amines which have been hydroxylated following dehydrogenation have also had tertiary carbons at both α- and β-positions to the nitrogen, such as 1-methylquinolizidine[3g] and 1-methyldecahydroquinoline.[3h]

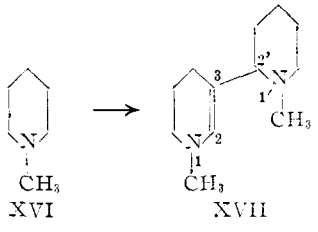
1-Methyl-2,2,6-trialkylpiperidines are oxidized by mercuric acetate at the tertiary α-carbon, on the basis of analogy with the models already cited (I, VIII, XI, XIV) and the observed fate of 2-benzyl-1,2,6-trimethylpiperidine (III) with this reagent. The tetrasubstituted piperidine III was oxidized to 6-benzyl-1,2,6-trimethyl-Δ^2-tetrahydropyridine, isolated as the salt IV, 6-benzyl-1,2,6-trimethyl-Δ^1-tetrahydropyridinium perchlorate. The oxidation may serve as one stage in the route to pentasubstituted piperidines, *e.g.*, V.

1-Methyl-2,2,6,6-tetraalkylpiperidines are resistant to oxidation by aqueous mercuric acetate, when their reactivity is compared with 1-methylpiperidines having incomplete α-carbon substitution. Thus, 1,2,2,6,6-pentamethylpiperidine gave no indication of reaction when maintained at steam-bath temperature for 3 hr. with mercuric acetate in 5% aqueous acetic acid (95% water). No mercurous acetate was precipitated, and a good recovery of the substrate was realized. When 2,6-dibenzyl-1,2,6-trimethylpiperidine (V) was used, some oxidation did occur, but it must be assumed the site of oxidation was the benzyl moiety or cleavage of the C_α–N bond.

Unsubstituted piperidine and pyrrolidine gave no indication of the occurrence of oxidation under the standard conditions.

Compounds of type $(CH_3)_2N$–CH< are represented by N,N-dimethylcyclohexylamine and N,N-dimethylbenzylamine, which yielded cyclohexanone and benzaldehyde, respectively. These results do not indicate an abnormal reaction so far as the mercuric acetate oxidation is concerned, since the ternary iminium salt which can be formed by oxidation at the tert.-α-carbon would not be stable to the potentially hydrolytic conditions.[23]

The simplest tertiary amine in the piperidine series, **1-methylpiperidine (XVI)**, gave the most spectacular result. The mercuric acetate oxidation of this compound gave 1,1′-dimethyl-Δ^2-tetrahydroanabasine (XVII) in 67% yield, open-



ing up a new synthetic route to compounds of the bipiperidine type. The product is less surprising when one considers it to be a "dimer" of the 1-methyl-Δ^2-tetrahydropyridine which would be the expected initial oxidation product of 1-methylpiperidine. The method of structure-proof and additional reactions of XVII will be discussed later in this article. Other 1-methylpiperidines unsubstituted at the 2- and 6-positions and those disubstituted at the 2-position also give tetrahydropyridines whose tendency to "dimerize" is a function, at least partially, of the ring substitution.

In comparing the mercuric acetate oxidation of all of the amines studied, the reaction conditions were kept as uniform as possible throughout the series. It was observed that the time required for the first visible amount of mercurous acetate to precipitate in the hot oxidation mixture was reproducible within 1–2 minutes in several runs with the same substituted piperidine, but varied irregularly from compound to compound. The highest yield of basic product isolated from any substituted piperidine was 79%, but the yield of unsaturated amine provided no direct correlation with the structure of the original saturated amine. The yield of mercurous acetate was qualitatively more indicative. Using the theoretical yield in the examples cited as that resulting from the removal of

(23) C. Mannich and F. Davidsen, *Ber.*, **69B**, 2106 (1936).

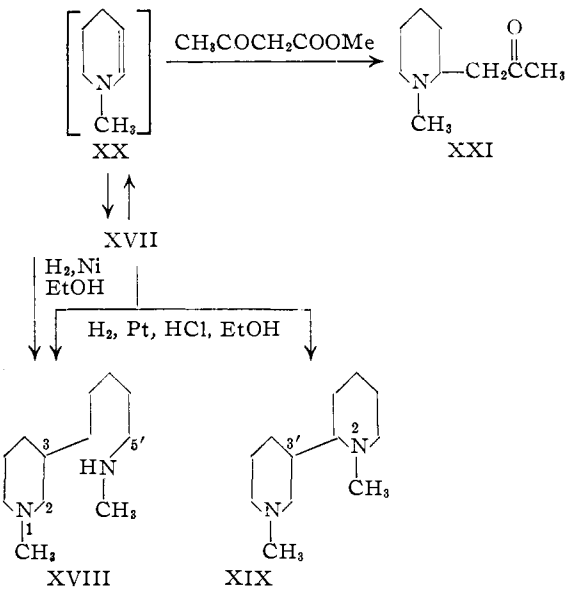
two hydrogens from the substituted piperidine, it was found that while all compounds which were monosubstituted at the 2-position gave low to theoretical yields, rather high values were observed with certain other compounds. The high value (40% over theoretical for 2H) for 1,3-dimethyl-2-ethylpiperidine reflects the hydroxylation reaction, and high values observed for 1-cyclohexylpiperidine and 1-cyclohexylpyrrolidine suggest further oxidation. 1,3-Substituted and 1,3,5-substituted piperidines also resulted in precipitation of mercurous acetate in excess of the theoretical amount.

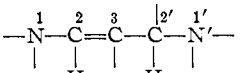
Substituted Δ^2-Tetrahydroanabasines. Formation and Structure

The establishment of the structure of the $(C_6H_{11}N)_2$ product isolated from the mercuric acetate oxidation of 1-methylpiperidine as 1,1′-dimethyl-Δ^2-tetrahydroanabasine (XVII) was simplified by the recent characterization of this compound by Schöpf and deWaal[24] and by the recognition that products derived from 1-methyl-Δ^2-tetrahydropyridine (XX) result from the reduction of 1-methyl-2-piperidone with sodium and butanol[25] or lithium aluminum hydride[26] and from the electrolytic reduction of N-methylglutarimide.[25] The formation of XVII may be visualized as resulting from the condensation of one molecule of 1-methyl-Δ^2-tetrahydropyridine in the hydrated form (pseudobase or aminoaldehyde) with a second molecule at the active methylenic 3-carbon of the ternary iminium acetate form.[24,27,28]

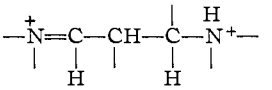
The dimeric nature of the 1-methylpiperidine oxidation product was indicated by its relatively high boiling point, and the presence of a double bond and the absence of a secondary amine grouping were recognized from the infrared spectrum. These facts, together with the elemental analysis and the ultraviolet transparency of the compound in ether solution above 217 mμ, were consistent with the 1,1′-dimethyl-Δ^2-tetrahydroanabasine formulation (XVII). The catalytic reduction of XVII according to the conditions cited by Schöpf and deWaal[29] was used for confirmation of the structure, both by means of the products formed and their dependency upon the medium employed: ethanol, Raney nickel; glacial acetic acid, platinum oxide; 1:1 ethanol–12 *N* hydrochloric acid, platinum oxide.[30]

The chief product of the reduction in acetic acid was 1-methyl-3-(5′-methylaminopentyl)-piperidine (XVIII), identical with the compound obtained by the method of Lukeš and Kovář,[25] the sodium–butanol reduction of 1-methyl-2-piperidone. The catalytic reduction in strong hydrochloric acid solution provided 24% of 1-methyl-3-(5′-methylaminopentyl)-piperidine (XVIII) and 61% of 1,1′-dimethyl-2,3′-bipiperidine (XIX).[25] In neutral or weak acid solution, the





system of VXII or its N-protonated form can be cleaved at the allylic $C_{2'}$–$N_{1'}$ linkage,[24] whereas in strong acid solution, any preferred residence in the ternary iminium salt form



would be expected to permit preservation of the $C_{2'}$–$N_{1'}$ linkage—and thus the bicyclic system–in the catalytic hydrogenation. The equilibrium between 1,1′-dimethyl-Δ^2-tetrahydroanabasine and the monomer 1-methyl-Δ^2-tetrahydropyridine (XX, or the corresponding pseudobase or aminoaldehyde form), at least in hydroxylic solvent, was demonstrated by the reaction of XVII with methyl acetoacetate in 50% aqueous methanol to yield, after decarboxylation, N-methylisopelletierine (XXI), identified by physical properties and derivatives. This trapping technique has been used by Galinovsky.[25,31] The present method, mercuric acetate oxidation of 1-methylpiperidine followed by condensation with an active methylene compound, provides a simple, efficient route to many compounds, of which N-methylisopelletierine is only one example.[31a]

Having established the structure of the dimeric product obtained on mercuric acetate oxidation of 1-methylpiperidine, we are in a position to make analogical structural assignments to the dimeric products, where these exhibit similar properties and

(24) C. Schöpf and H. L. deWaal, *Chem. Ber.*, **89**, 909 (1956).

(25) R. Lukeš and K. Kovář, *Coll. Czech. Chem. Commun.*, **19**, 1215, 1227 (1954).

(26) F. Galinovsky, A. Wagner and R. Weiser, *Monatsh. Chem.*, **82**, 551 (1951).

(27) C. Schöpf, P. Braun and A. Komzak, *Chem. Ber.*, **89**, 1821 (1956).

(28) C. Schöpf, *Z. angew. Chem.*, **59**, 29 (1947).

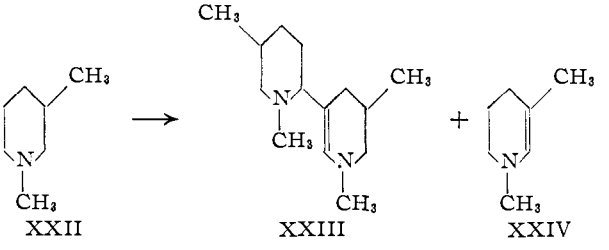
(29) Reference 24, footnote 26; see also ref. 26.

(30) C. Schöpf, H. Arm, G. Benz and H. Krimm, *Naturwissen.*, **38**, 186 (1951).

(31) F. Galinovsky, *Monatsh. Chem.*, **82**, 551 (1951); see also R. Lukeš, J. Kovář, K. Bláha and J. Kloubek, *Coll. Czech. Chem. Commun.*, **21**, 1324 (1956).

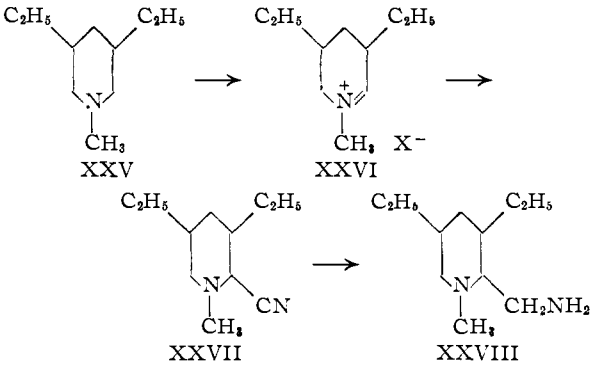
(31a) ADDED IN PROOF.—A contemporary submission by C. Schöpf, G. Herbert, R. Rausch and G. Schröder has appeared in *Angew. Chem.*, **69**, 391 (1957), describing another route to 1,1′-dimethyl-Δ^2-tetrahydroanabasine(XVII) and its conversion to N-methylisopelletierine.

reactions, obtained on oxidation of other substituted piperidines. For example, 1-benzylpiperidine yielded (39%) 1,1'-dibenzyl-Δ^2-tetrahydroanabasine. 1,3-Dimethylpiperidine (XXII), subjected to mercuric acetate treatment, yielded a high boiling product with analysis and properties suggestive of 1,1',5,5'-tetramethyl-Δ^2-tetrahydroanabasine (XXIII), the result of oxidation on the unsubstituted side of the piperidine ring followed by coupling of two 1,5-dimethyl-Δ^2-tetrahydropyridine units. The low boiling fraction of the crude oxidation product contained some 1,3-dimethyl-Δ^2-tetrahydropyridine (XXIV), the result of oxidation on the methyl-substituted side of the ring, as indicated by infrared spectral comparison with an authentic sample of XXIV.[17]



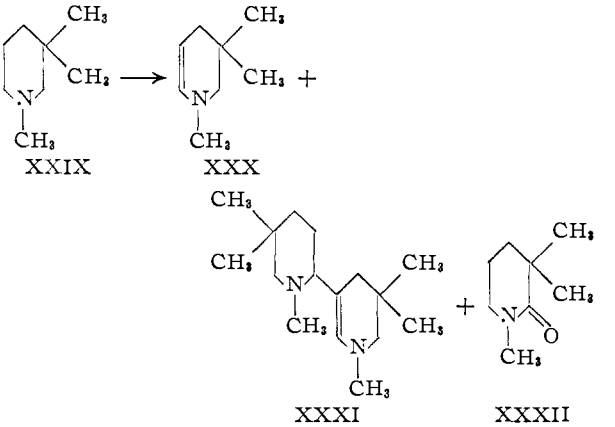
XXII XXIII XXIV

Oxidation of 3,5-diethyl-1-methylpiperidine (XXV) with mercuric acetate furnished 3,5-diethyl-1-methyl-Δ^2-tetrahydropyridine (61% yield), which provided a unique example of an enamine unsubstituted on the α-carbon yet incapable of dimerization. The related ternary iminium salt, 3,5-diethyl-1-methyl-Δ^1-tetrahydropyridinium perchlorate (XXVI), underwent reaction with benzylmagnesium chloride to give 2-benzyl-3,5-diethyl-1-methylpiperidine and with aqueous potassium cyanide to give 2-cyano-3,5-diethyl-1-methylpiperidine (XXVII). Reduction of XXVII with lithium aluminum hydride produced the diamine XXVIII, 2-aminomethyl-3,5-diethyl-1-methylpiperidine, in 96% yield. This behavior of a sec.-α_N-nitrile group with lithium aluminum hydride is in marked contrast to the replacement of tert.-α_N-nitrile groups described earlier.

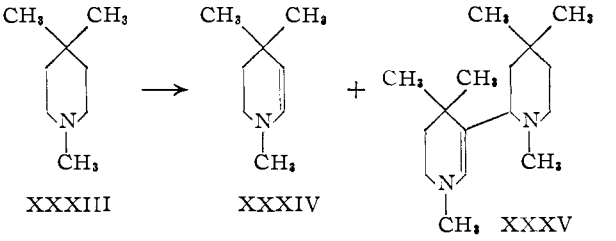


XXV XXVI XXVII XXVIII

gem-Dimethyl substitution on the piperidine ring appears to provide some steric stabilization of a monomeric α-unsubstituted enamine and its salt, judging from the products obtained from the mercuric acetate oxidation of 1,3,3-trimethylpiperidine (XXIX). Thus, the basic components consisted of 1,5,5-trimethyl-Δ^2-tetrahydropyridine (XXX), convertible to 1,5,5-trimethyl-Δ^1-tetrahydropyridinium perchlorate, and 1,1',5,5,5',5'-hexamethyl-Δ^2- tetrahydroanabasine (XXXI). The neutral component of the crude oxidation product was also sought in this case and was shown to be 1,3,3-trimethyl-2-piperidone (XXXII) (15% yield). Mercuric acetate oxidation of 1,4,4-trimethylpiperidine (XXXIII) furnished a mixture of 1,4,4-trimethyl-Δ^2-tetrahydropyridine (XXXIV) and 1,1',4,4,4',4'-hexamethyl-Δ^2-tetrahydroanabasine (XXXV), in which the former was the major component. Conversion of XXXIV to the perchlorate salt, followed by reaction with potassium cyanide and hydride reduction of the aminonitrile, was parallel to the sequence observed for 3,5-diethyl-1-methyl-Δ^2-tetrahydropryidine. Even 1-ethyl-4-methylpiperidine gave an oxidized mixture from which some 1-ethyl-4-methyl-Δ^2-tetrahydropyridine could be isolated along with the major dimeric component.



XXIX XXX XXXI XXXII



XXXIII XXXIV XXXV

Infrared Spectra of Substituted Δ^2-Tetrahydropyridines and their Salts

The mercuric acetate oxidation of substituted piperidines has provided a number of tetrahydropyridines, for which the infrared spectra as free bases and as salts provide useful information applicable to the characterization of enamines. The generality[3a] has been sustained that there is a decided shift toward higher frequency of the double bond stretching maximum in going from an α,β-unsaturated amine to the corresponding (ternary iminium) salt, as shown in Table I. Compounds with small alkyl substituents on the 1- and 2-positions show large shifts. Examples in which salt formation involves a conjugated double bond also show large shifts. In one example a very small shift was observed, that of 6-benzyl-1,2,6-trimethyl-Δ^2-tetrahydropyridine, which has a highly substituted 6-position. It may be seen from Table I that the wave number at which the double bond maximum is found for the enamines in this series

shows a dependence upon the substitution on the double bond, which may be of some restricted application. Thus, 2-alkyl-substituted compounds absorb in the region 1645–1652 cm.$^{-1}$; 3-substituted, 1666–1673 cm.$^{-1}$; unsubstituted on the double bond, 1638–1648 cm.$^{-1}$.

TABLE I

DOUBLE BOND STRETCHING MAXIMA IN THE INFRARED SPECTRA OF α,β-UNSATURATED AMINES AND THEIR PERCHLORATES

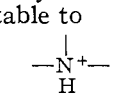
Δ^2-Tetrahydropyridine	νmax., cm.$^{-1}$[a] Base[b]	Perchlorate[c,d]
1,2-Dimethyl-	1649	1690
2-Ethyl-1-methyl-	1645	1683
1,2-Diethyl-	1646	1671
2-Benzyl-1-methyl	1645(m) 1615[e]	1672
2-Phenyl-1-methyl-	1630[f]	1691(m) 1671
1,2,6-Trimethyl-	1650	1679
2,6-Diethyl-1-methyl-	1649	1667
1,2-Dimethyl-5-ethyl-	1652	1694
1,2,3-Trimethyl	1657	1682
1,3-Dimethyl-2-ethyl-	1649	1669
6-Benzyl-1,2,6-trimethyl-	1648	1652
1,3-Dimethyl-	1673	1698[g]
1,5-Dimethyl-	1648[h]	..
3,5-Diethyl-1-methyl-	1666	1700[i]
1,5,5-Trimethyl-	1652(m)[j]	1697[k]
1,4,4-Trimethyl-	1645	1707[l]
1-Ethyl-4-methyl-	1640	1690[m]

[a] Strong unless otherwise indicated. [b] Liquid film. [c] Nujol mull. [d] Ternary iminium form unless otherwise indicated. [e] Indicative of two forms of the base, the maximum at 1615 cm.$^{-1}$ probably corresponding to that in which the double bond is exocyclic to the piperidine ring, conjugated with phenyl. The perchlorate salt is unique, with the double bond in the ternary iminium location. [f] Indicative of conjugation with phenyl. [g] Additional maxima were also observed.[17] [h] Detected in mixture. [i] Additional weak bands at 3080, 2180, 2010 cm.$^{-1}$. [j] Not completely purified. [k] Additional bands at 1625, 3080 cm.$^{-1}$. [l] Additional bands at 3070, 3000, 2180, 2015 cm.$^{-1}$. [m] Oil, additional bands at 3080, 1602 cm.$^{-1}$.

While only two 2,3-substituted examples are available, these absorb at wave numbers between those for corresponding 1,2- and 1,3-disubstituted compounds. Among the perchlorate salts, those which bear no 2-substituents absorb at distinctly higher wave numbers than those bearing 2-substituents. On the basis of only three compounds studied, the ternary iminium picrates absorb 5–10 cm.$^{-1}$ lower than the corresponding perchlorates (both in Nujol mull).

No evidence for an ammonium salt form was found in the spectrum of the perchlorate or picrate of any tetrahydropyridine with a substituent on the 2-position. However, a number of the salts having no 2-substitution exhibit bands attributable to

and C=C. The most extreme case studied was the perchlorate of 1-ethyl-4-methyl-Δ^2-tetrahydropyridine, which was an oil in contrast to the other salts studied, with an infrared spectrum suggestive of a mixture of N-protonated salt (3080(s), 1602(m) cm.$^{-1}$) and C-protonated salt (1690(m) cm.$^{-1}$). In like manner, the spectra of the perchlorate salts of 1,5,5-trimethyl-, 1,4,4,-trimethyl-, 1,3-dimethyl- and 3,5-diethyl-1-methyl-Δ^2-tetrahydropyridine exhibit bands attributable to



in addition to the expected >C=$\overset{+}{\text{N}}$< maxima.

In terms of chemical properties, the most useful diagnostic reaction of the ternary iminium salts has been found to be their efficient conversion to aminonitriles with potassium cyanide. Moreover, the reduction of these nitriles with lithium aluminum hydride has provided a useful method for distinguishing between 2-cyano-1,2-dimethylpiperidines and 2-cyano-1-methylpiperidines.[32] The use of the Lipp reaction,[33] which depends upon the partial hydrolysis of enamines in solution, as a chemical method for determining the type of enamine function present in a tetrahydropyridine is definitely restricted. Thus, while 1,2-dimethyl-Δ^2-tetrahydropyridine gave 3-acetyl-1-methylpiperidine in 52% yield on treatment in the cold with formalin, 1,2-dimethyl-5-ethyl-Δ^2-tetrahydropyridine gave 3-acetyl-5-ethyl-1-methylpiperidine in only 23% yield along with a large amount of high boiling material.

Experimental[34]

Saturated Amines.[35]—The following known saturated tertiary amines were used as precursors or for characterization during the course of the present investigation: 1-benzylpiperidine,[36] b.p. 134–136° (20 mm.), n^{20}D 1.5242; chloroplatinate, m.p. 191–193°; 1-cyclohexylpiperidine,[37,38] b.p. 123–125° (20 mm.), n^{22}D 1.4826; picrate,[39] m.p. 132–133°; 1-cyclohexylpyrrolidine,[40] b.p. 95–97° (18 mm.), n^{21}D 1.4804; picrate, m.p. 163–165°; 1-cyclopentylpiperidine,[41] b.p. 205–208° (745 mm.), n^{21}D 1.4800; picrate,[42] m.p. 171.5–172.5°; 2,2-diethyl-1-methylpiperidine,[191] b.p. 172–174° (745 mm.), n^{21}D 1.4670; picrate, m.p. 227–228° dec.; N,N-dimethylbenzylamine,[43] b.p. 79–80° (20 mm.), n^{20}D 1.5002; chloroplatinate, m.p. 190–192°; N,N-dimethylcyclohexylamine,[44] b.p. 156–158° (740 mm.), n^{22}D 1.4527; picrate, m.p. 177–178°; 1,2-dimethylpiperidine,[45] b.p. 123–124° (745 mm.); n^{20}D 1.4413; picrate, m.p. 240–242°; 1,3-dimethylpiperidine,[46] b.p. 123–124° (745 mm.), n^{25}D 1.4320; picrate, m.p. 167–168°; 2-ethyl-1-methylpiperidine,[47] b.p. 150–152° (745 mm.), n^{20}D 1.4495; picrate,

(32) See also: L. H. Amundsen and L. S. Nelson, THIS JOURNAL, **73**, 242 (1951); H. E. Zaugg and B. W. Horrom, *ibid.*, **75**, 292 (1953); Z. Welvart, *Compt. rend.*, **233**, 1121 (1951); **239**, 1299 (1954); Abstract No. 114, XIVth International Congress of Pure and Applied Chemistry, Zürich, Switzerland, July, 1955.

(33) A. Lipp, *Ber.*, **25**, 2197 (1892).

(34) We are indebted to Mrs. Esther Fett, Mrs. Lucy Chang, Mrs. R. Maria Benassi, Mrs. Ruby Ju, Miss Claire Higham, Mr. Jozsef Nemeth and Mr. R. J. Nesset for microanalyses, to Mrs. Louise Griffing and Mr. James Brader for determination of the infrared absorption spectra and to Miss Gerardine Meerman for determination of the ultraviolet absorption spectra.

(35) We are grateful to Eli Lilly and Co., Indianapolis, Ind., for a generous gift of several important precursors for this series.

(36) J. von Braun, *Ber.*, **37**, 2915 (1904).

(37) C. F. Winans and H. Adkins, THIS JOURNAL, **54**, 306 (1932).

(38) P. A. S. Smith and A. J. MacDonald, *ibid.*, **72**, 1037 (1950).

(39) J. F. Bunnett and J. L. Marks, *ibid.*, **71**, 1587 (1949).

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(41) J. Loevenich, H. Utsch, P. Moldrickx and E. Schaefer, *Ber.*, **62B**, 3084 (1929).

(42) J. I. Jones, *J. Chem. Soc.*, 1392 (1950).

(43) A. Skita and F. Keil, *Ber.*, **63**, 34 (1930).

(44) P. Sabatier and J. B. Senderens, *Comp. rend.*, **138**, 1257 (1904).

(45) K. N. Campbell, F. C. Factora, Jr., and B. K. Campbell, *J. Org. Chem.*, **17**, 1141 (1952).

(46) A. Ladenburg, *Ann.*, **247**, 1 (1888).

(47) A. Lipp, *Ber.*, **33**, 3513 (1900).

m.p. 172–174°; 1-methylpiperidine,[36] b.p. 104–105° (745 mm.), n^{20}D 1.4370; picrate, m.p. 224–225°; 1,2,2-trimethylpiperidine,[19b,1] picrate, m.p. 275° dec.; 1,2,6-trimethylpiperidine,[48] b.p. 144–145° (745 mm.), n^{20}D 1.4462; picrate,[49] m.p. 227–228°.

Mercuric Acetate Oxidation of 1,2-Dimethylpiperidine. General Procedure for Mercuric Acetate Oxidations.—A mixture of 11.3 g. (0.10 mole) of 1,2-dimethylpiperidine and 150 g. (0.48 mole) of mercuric acetate in 400 ml. of 5% acetic acid (95% water) was heated on the steam-bath with stirring for 2 hr. The first precipitate appeared 15 minutes after heating was begun. The reaction mixture was cooled, and the precipitated mercurous acetate was collected by filtration and washed with 5% acetic acid (washings added to filtrate), then with acetone (washings discarded). The precipitate, dried by suction on the filter, weighed 46 g. The filtrate was saturated with hydrogen sulfide, and subsequent filtration was carried out using a previously formed mat of wet Filter-Cel over a filter paper in a büchner funnel large enough to hold the entire mixture at once. The mercuric sulfide was washed with dilute acetic acid, and the combined filtrates were resaturated with hydrogen sulfide. The subsequent filtrate was basified with solid potassium carbonate added in small portions. When no more gas evolution occurred, a layer of ether was added, and the aqueous layer was treated with more potassium carbonate to saturation. The layers were separated, and the aqueous layer was extracted with additional portions of ether. The combined extracts were dried over magnesium sulfate for a short time, filtered, and to the filtrate was added about 5% of its volume of ethanol. A solution of 1:1 65% perchloric acid:ethanol was added dropwise with swirling until the mixture was acid to Congo red. The colorless solid was collected by filtration and was washed with a little ethanol. Recrystallization from ethanol yielded 9.8 g. (45%) of colorless needles of **1,2-dimethyl-Δ¹-tetrahydropyridinium perchlorate**, m.p. 228–229°.[3a,19c]

Anal. Calcd. for $C_7H_{14}ClNO_4$: C, 39.73; H, 6.66; N, 6.62. Found: C, 39.57; H, 6.59; N, 6.87.

The free base, 1,2-dimethyl-Δ²-tetrahydropyridine,[7] was obtained from the perchlorate salt by basification with potassium carbonate under ether, further extraction with ether, drying the combined ether extracts, removal of the ether and distillation of the residue from sodium under nitrogen, b.p. 129–130° (745 mm.), n^{22}D 1.4832.[19c]

General Reactions Illustrated with 1,2-Dimethyl-Δ²-tetrahydropyridine and its Derivatives. a. Reaction of Methylmagnesium Iodide with 1,2-Dimethyl-Δ¹-tetrahydropyridinium Perchlorate.—To the solution of the Grignard reagent prepared from 30 g. of methyl iodide and 5.2 g. of magnesium in 200 ml. of dry ether was added 100 ml. of anhydrous benzene. Solvent was removed by distillation until the vapor temperature reached about 72°. The solution was cooled in an ice-bath while 4.8 g. (0.027 mole) of 1,2-dimethyl-Δ¹-tetrahydropyridinium perchlorate was added all at once. Some gas evolution was noted. The mixture was heated under reflux for 6 hr., decomposed with dilute hydrochloric acid, rendered strongly basic with sodium hydroxide and subjected to steam distillation. The distillate was saturated with sodium chloride and extracted with several portions of ether. The combined extracts were dried over magnesium sulfate, and the solution was treated with ethanolic picric acid. The picrate, obtained in low yield, had the properties, including m.p. 275° dec., described[19b,1] for this derivative of **1,2,2-trimethylpiperidine**.

b. Reaction of Benzylmagnesium Chloride with 1,2-Dimethyl-Δ¹-tetrahydropyridinium Perchlorate.—To the ice-cold Grignard reagent prepared from 12.6 g. (0.10 mole) of benzyl chloride and 2.7 g. of magnesium in 150 ml. of anhydrous ether was added 5.5 g. (0.026 mole) of 1,2-dimethyl-Δ¹-tetrahydropyridinium perchlorate. The mixture was stirred in the cold for a few minutes, then heated at reflux for 2 hr. No precipitate formed during that time. The mixture was decomposed with dilute hydrochloric acid, the layers were separated and the aqueous layer was basified under ether with potassium carbonate. Isolated in the usual manner from the ether extracts, the **2-benzyl-1,2-dimethylpiperidine**, b.p. 189–190° (60 mm.), n^{20}D 1.5330, was obtained in 82% yield (4.30 g.).

The **picrate** crystallized from ethanol as yellow prisms, m.p. 157–159°.

Anal. Calcd. for $C_{20}H_{24}N_4O_7$: C, 55.55; H, 5.59; N, 12.96. Found: C, 55.53; H, 5.53; N, 13.14.

c. Reaction of Potassium Cyanide with 1,2-Dimethyl-Δ¹-tetrahydropyridinium Perchlorate.—To a solution of 10.0 g. (0.052 mole) of 1,2-dimethyl-Δ¹-tetrahydropyridinium perchlorate in 75 ml. of water in a small separatory funnel was added 9.5 g. (0.15 mole) of potassium cyanide and a portion of ether. The mixture was shaken vigorously and extracted with further portions of ether. The combined ether extracts were dried and concentrated. The residue of **2-cyano-1,2-dimethylpiperidine** was distilled, b.p. 84–86° (18 mm.), n^{20}D 1.4572, yield 6.3 g. (97%).

Anal. Calcd. for $C_8H_{14}N_2$: C, 69.52; H, 10.21; N, 20.27. Found: C, 69.65; H, 10.03; N, 20.36.

The infrared spectrum of a liquid film exhibited a sharp maximum of low intensity at 2220 cm.$^{-1}$ and no maximum in the 6 μ region.

d. Reaction of Methylmagnesium Iodide with 2-Cyano-1,2-dimethylpiperidine.—To the ice-cold Grignard reagent prepared from 16.5 g. (0.116 mole) of methyl iodide and 3.10 g. (0.127 gram atom) of magnesium in 50 ml. of anhydrous ether was added a solution of 3.0 g. (0.024 mole) of 2-cyano-1,2-dimethylpiperidine in 50 ml. of ether. The solution was heated at reflux for 2 hr. and worked up in the manner described above to give 2.8 g. (36%) of **1,2,2-trimethylpiperidine picrate**, m.p. 273–275° dec.[19b,1]

e. Lithium Aluminum Hydride Reduction of 2-Cyano-1,2-dimethylpiperidine.—A slurry of 2.3 g. (0.061 mole) of lithium aluminum hydride in 100 ml. of dry ether was cooled in ice and stirred while a solution of 5.8 g. (0.042 mole) of 2-cyano-1,2-dimethylpiperidine in 75 ml. of anhydrous ether was added dropwise. The mixture was stirred in the cold for 30 minutes and then at reflux for 3 hr. Excess reagent was decomposed by the cautious dropwise addition of a saturated aqueous solution of potassium carbonate. The powdery precipitate that was formed was collected on a sintered-glass funnel and washed several times with ether. The combined ethereal filtrates were concentrated, and the residual oil was converted to the picrate: **1,2-dimethylpiperidine picrate**, m.p. 240–242°,[45] yield 8.5 g. (60%).

f. Reaction of 1,2-Dimethyl-Δ²-tetrahydropyridine with Formaldehyde.—To an ice-cold solution of 9.15 g. (0.082 mole) of 1,2-dimethyl-Δ²-tetrahydropyridine in 100 ml. of water maintained under nitrogen was added slowly a solution of 6.55 g. (0.082 mole) of 37% formalin in 25 ml. of water. Stirring was continued in the cold for several hours, and the solution was allowed to come up to room temperature overnight. The reaction mixture was acidified with hydrochloric acid, concentrated to small volume and extracted with ether to remove any non-basic impurities. Basification of the aqueous layer with sodium hydroxide solution under ether was followed by repeated ether extraction. These ether extracts were combined, dried and concentrated, and the residual liquid was distilled through a Holzman column and identified as **3-acetyl-1-methylpiperidine**,[33] b.p. 91–92° (18 mm.), n^{21}D 1.4616, yield 5.91 g. (52%); hydrochloride, colorless prisms from ethanol–ether, m.p. 157–158°; phenylhydrazone hydrochloride, colorless prisms from ethanol–ether, m.p. 205–207°.[50]

Mercuric Acetate Oxidation of 2-Ethyl-1-methylpiperidine. 2-Ethyl-1-methyl-Δ²-tetrahydropyridine.—Oxidation of 12.7 g. (0.10 mole) of 2-ethyl-1-methylpiperidine[47] by the general procedure described gave 12.9 g. (57%) of **2-ethyl-1-methyl-Δ¹-tetrahydropyridinium perchlorate**, colorless needles from ethanol, m.p. 240° (reported[191] 237°). No depression in melting point was observed on admixture with an authentic sample prepared as described below. The free base was liberated in the usual manner: **2-ethyl-1-methyl-Δ²-tetrahydropyridine**,[191] b.p. 154° (745 mm.), n^{23}D 1.4808.

Reaction of Grignard Reagents with 1-Methyl-2-piperidone. a. Ethylmagnesium Iodide.—The procedure was essentially that of Lukeš and Grossmann.[191] The products were separated as follows. The combined and dried ether extracts resulting from the usual isolation procedure were treated with ethanolic perchloric acid. The precipitate, which was recrystallized from ethanol as colorless needles, m.p. 237–239° dec., yield 37%, consisted of **2-ethyl-1-methyl-Δ¹-tetrahydropyridinium perchlorate**. The by-product of **2,2-diethyl-1-methylpiperidine**[191] was isolated

(48) R. A. Robinson, *J. Org. Chem.*, **16**, 1911 (1951).

(49) T. D. Perrine, *ibid.*, **16**, 1303 (1951).

(50) A. Lipp and E. Widnmann, *Ber.*, **38**, 2471 (1905).

from the ether–ethanol mother liquors by a sequence of basification, extraction and distillation, b.p. 172–174°, $n^{21}D$ 1.4670, yield 19%. The same product was obtained by the reaction of ethylmagnesium iodide with 2-ethyl-1-methyl-Δ^1-tetrahydropyridinium perchlorate and was isolated as **2,2-diethyl-1-methylpiperidine picrate**, m.p. 227–228° dec. (reported[191] 224°), yellow prisms from ethanol.

Anal. Calcd. for $C_{16}H_{24}N_4O_7$: C, 49.99; H, 6.29; N, 14.58. Found: C, 50.12; H, 6.35; N, 14.52.

b. Phenylmagnesium Bromide.—A simplified procedure adapted from Lukeš and Grossmann[191] was used to obtain the perchlorate of 1-methyl-2-phenyl-Δ^2-tetrahydropyridine in 91% yield, m.p. 146–147° (reported[191] 146.5°), converted to the free base, b.p. 127–128° (18 mm.) (reported [191] 139° (20 mm.)).

c. Benzylmagnesium Chloride.—The procedure provided **2-benzyl-1-methyl-Δ^1-tetrahydropyridinium perchlorate** in 94% yield, m.p. 134–135° (reported[191] 135°), colorless plates from ethanol. The corresponding free base had b.p. 169° (25 mm.).[191]

The general procedure for the addition of Grignard reagents to ternary iminium salts was followed in the combination of benzylmagnesium chloride with 2-benzyl-1-methyl-Δ^1-tetrahydropyridinium perchlorate to give **2,2-dibenzyl-1-methylpiperidine** in 74% yield, m.p. 100°, colorless needles from ether.

Anal. Calcd. for $C_{20}H_{25}N$: C, 85.97; H, 9.02; N, 5.01. Found: C, 85.84; H, 8.99; N, 4.95.

2,2-Dibenzyl-1-methylpiperidine perchlorate crystallized from ethanol as colorless prisms, m.p. 175–176°.

Anal. Calcd. for $C_{20}H_{26}ClNO_4$: C, 63.23; H, 6.89; N, 3.69. Found: C, 63.12; H, 6.94; N, 3.49.

2,2-Dibenzyl-1-methylpiperidine picrate crystallized from ethanol as yellow prisms, m.p. 200–201°.

Anal. Calcd. for $C_{26}H_{28}N_4O_7$: C, 61.47; H, 5.55; N, 11.02. Found: C, 61.53; H, 5.88; N, 11.31.

Mercuric Acetate Oxidation of 1,2-Diethylpiperidine.[51] **1,2-Diethyl-Δ^2-tetrahydropyridine.**—Alkylation of 2-ethylpiperidine with ethyl iodide in ethanol using potassium carbonate furnished 1,2-diethylpiperidine in 78% yield, b.p. 76–80° (32 mm.), $n^{20}D$ 1.4530. **The picrate** crystallized from ethanol as yellow plates, m.p. 130–131°.

Anal. Calcd. for $C_{15}H_{22}N_4O_7$: C, 48.64; H, 5.99; N, 15.13. Found: C, 49.00; H, 6.11; N, 15.20.

Mercuric acetate oxidation of 1,2-diethylpiperidine by the general procedure furnished **1,2-diethyl-Δ^1-tetrahydropyridinium perchlorate**, m.p. 260–262° dec., colorless needles from ethanol, in 44% yield.

Anal. Calcd. for $C_9H_{18}ClNO_4$: C, 45.09; H, 7.58; N, 5.85. Found: C, 45.22; H, 7.35; N, 5.74.

1,2-Diethyl-Δ^2-tetrahydropyridine had b.p. 70° (20 mm.).

Anal. Calcd. for $C_9H_{17}N$: C, 77.63; H, 12.31. Found: C, 77.03; H, 12.10.

Addition of ethylmagnesium iodide to 1,2-diethyl-Δ^1-tetrahydropyridinium perchlorate yielded **1,2,2-triethylpiperidine**, b.p. 70–71° (20 mm.), $n^{22}D$ 1.4610. **The picrate** crystallized from ethanol as yellow prisms, m.p. 128–129°.

Anal. Calcd. for $C_{17}H_{26}N_4O_7$: C, 51.25; H, 6.58; N, 14.06. Found: C, 51.35; H, 6.54; N, 13.70.

Mercuric Acetate Oxidation of 1,2,6-Trimethylpiperidine. 1,2,6-Trimethyl-Δ^2-tetrahydropyridine.—Oxidation of 1,2,6-trimethylpiperidine[48] by the general procedure gave **1,2,6-trimethyl-Δ^1-tetrahydropyridinium perchlorate**, m.p. 201–202°, colorless needles from ethanol, in 66% yield.

Anal. Calcd. for $C_8H_{16}ClNO_4$: C, 42.56; H, 7.15; N, 6.21. Found: C, 42.83; H, 7.44; N, 6.17.

1,2,6-Trimethyl-Δ^2-tetrahydropyridine obtained from the perchlorate salt had b.p. 146°, $n^{22}D$ 1.4740.

Anal. Calcd. for $C_8H_{15}N$: C, 76.74; H, 12.08; N, 11.19. Found: C, 76.21; H, 11.76; N, 11.03.

The picrate crystallized as orange-yellow prisms from ethanol, m.p. 194°, and exhibited infrared maxima (Nujol mull) at 1673(m), 3060(w) and 3000(w) cm.$^{-1}$, in addition to the usual picrate bands.

Anal. Calcd. for $C_{14}H_{18}N_4O_7$: C, 47.45; H, 5.12; N, 15.81. Found: C, 47.63; H, 5.13; N, 16.17.

1,2,6-Trimethyl-Δ^1-tetrahydropyridinium perchlorate did not appear to undergo addition with methylmagnesium iodide, methyllithium or ethyl bromozincacetate but did react with benzylmagnesium chloride to give **2-benzyl-1,2,6-trimethylpiperidine**, b.p. 153–154° (18 mm.), $n^{20}D$ 1.5280, in 96% yield, isolated as the perchlorate, m.p. 177–179°, colorless prisms from water.

Anal. Calcd. for $C_{15}H_{24}ClNO_4$: C, 56.69; H, 7.61; N, 4.41. Found: C, 56.98; H, 7.72; N, 4.30.

Reaction of Potassium Cyanide with 1,2,6-Trimethyl-Δ^1-tetrahydropyridinium Perchlorate.—By the procedure decribed for 2-cyano-1,2-dimethylpiperidine, combination of 4.50 g. (0.020 mole) of 1,2,6-trimethyl-Δ^1-tetrahydropyridinium perchlorate with excess potassium cyanide yielded 2.47 g. (82%) of **2-cyano-1,2,6-trimethylpiperidine**, b.p. 102–103° (23 mm.), $n^{20}D$ 1.4615, infrared maximum (liquid film) at 2220 cm.$^{-1}$, no 6 μ absorption.

Anal. Calcd. for $C_9H_{16}N_2$: C, 71.01; H, 10.60; N, 18.40. Found: C, 71.00; H, 10.65; N, 18.36.

The procedure outlined for the reaction of methylmagnesium iodide with 2-cyano-1,2-dimethylpiperidine when applied to 2-cyano-1,2,6-trimethylpiperidine gave mainly 1,2,6-trimethyl-Δ^2-tetrahydropyridine and a highly variable yield of **1,2,2,6-tetramethylpiperidine**, isolated as the **picrate**, m.p. 205° dec., yellow plates from ethanol.

Anal. Calcd. for $C_{15}H_{22}N_4O_7$: C, 48.64; H, 5.99; N, 15.13. Found: C, 48.78; H, 5.98; N, 15.42.

2,6-Diethyl-1-methylpiperidine.—A solution of 150 g. (2.22 moles) of methylamine hydrochloride and 300 g. (2.06 moles) of acetonedicarboxylic acid[52] in 3.5 l. of water was treated with 400 g. (6.90 moles) of propionaldehyde. Stirring at 25° overnight was followed by heating on the steam-bath for 10 hr. The low-boiling components were distilled, and the residual solution was acidified and cooled. A small amount of insoluble oil was removed by ether extraction, and the aqueous residue was made strongly basic by the addition of solid potassium hydroxide. The oily product was extracted with ether. The extracts were dried and the ether was removed. 2,6-Diethyl-1-methyl-4-piperidone was obtained on distillation (with much foaming) as a colorless oil, b.p. 128–130° (22 mm.), yield 110 g. (32%). A mixture of this crude aminoketone, 200 g. of potassium hydroxide, 65 ml. of hydrazine hydrate and 800 ml. of diethylene glycol was heated at 110–120° for 8 hr., after which the temperature was raised gradually to 190–210°. Distillate was collected while the temperature was maintained at this level for 3 hr. Steam distillation of the pot residue furnished additional material. The combined distillates were saturated with sodium chloride and extracted with ether. **2,6-Diethyl-1-methylpiperidine** was recovered from the ether extracts and purified by distillation from sodium, b.p. 87–89° (22 mm.), $n^{19}D$ 1.4572, yield 72 g. (72%). **The picrate** crystallized from ethanol as yellow prisms, m.p. 101–102°.

Anal. Calcd. for $C_{16}H_{24}N_4O_7$: C, 49.99; H, 6.29; N, 14.58. Found: C, 50.13; H, 6.44; N, 14.88.

Mercuric Acetate Oxidation of 2,6-Diethyl-1-methylpiperidine.—Application of the general procedure to 2,6-diethyl-1-methylpiperidine gave **2,6-diethyl-1-methyl-Δ^1-tetrahydropyridinium perchlorate** in 48% yield, m.p. 150–151°, colorless plates from ethanol.

Anal. Calcd. for $C_{10}H_{20}ClNO_4$: C, 47.34; H, 7.95; N, 5.52. Found: C, 47.36; H, 7.82; N, 5.40.

2,6-Diethyl-1-methyl-Δ^2-tetrahydropyridine was isolated from this salt, b.p. 85–87° (18 mm.), $n^{25}D$ 1.4718.

Anal. Calcd. for $C_{10}H_{19}N$: C, 78.36; H, 12.50; N, 9.14. Found: C, 78.20; H, 12.33; N, 8.97.

1,2-Dimethyl-5-ethylpiperidine.—Methylation of 5-ethyl-2-methylpiperidine[53] with formic acid and formalin produced 1,2-dimethyl-5-ethylpiperidine in 92% yield, b.p. 166–167° (745 mm.), $n^{22}D$ 1.4462.

Anal. Calcd. for $C_9H_{19}N$: C, 76.52; H, 13.56; N, 9.92. Found: C, 76.49; H, 13.48; N, 9.98.

(51) These experiments were carried out originally by Dr. A. S. Hay (see Ph.D. Thesis, University of Illinois, 1955).

(52) R. C. Menzies and R. Robinson, *J. Chem. Soc.*, **125**, 2163 (1924).

(53) J. von Braun, G. Lemke and A. Nelken, *Ber.*, **56**, 1364 (1923).

The picrate crystallized as yellow needles from ethanol, m.p. 166–168°.

Anal. Calcd. for $C_{15}H_{22}N_4O_7$: C, 48.64; H, 5.99; N, 15.13. Found: C, 48.68; H, 6.22; N, 15.01.

Mercuric Acetate Oxidation of 1,2-Dimethyl-5-ethylpiperidine.—Application of the general procedure to 1,2-dimethyl-5-ethylpiperidine gave **1,2-dimethyl-5-ethyl-Δ¹-tetrahydropyridinium perchlorate** in 66% yield, m.p. 150–151°, colorless plates from ethanol.

Anal. Calcd. for $C_9H_{18}ClNO_4$: C, 45.09; H, 7.57; N, 5.86. Found: C, 45.25; H, 7.68; N, 5.83.

1,2-Dimethyl-5-ethyl-Δ²-tetrahydropyridine had b.p. 183° (745 mm.), $n^{21}D$ 1.4750.

Anal. Calcd. for $C_9H_{17}N$: C, 77.63; H, 12.31. Found: C, 77.24; H, 12.36.

The reaction of excess potassium cyanide with 1,2-dimethyl-5-ethyl-Δ¹-tetrahydropyridinium perchlorate gave **2-cyano-1,2-dimethyl-5-ethylpiperidine** in 91% yield, b.p. 109° (18 mm.), $n^{21}D$ 1.4580, infrared maximum (liquid film) at 2220 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{18}N_2$: C, 72.24; H, 10.91; N, 16.85. Found: C, 71.84; H, 10.66; N, 16.67.

Lithium aluminum hydride reconverted 2-cyano-1,2-dimethyl-5-ethylpiperidine efficiently (86% yield) to 1,2-dimethyl-5-ethylpiperidine.

Reaction of 1,2-Dimethyl-5-ethyl-Δ²-tetrahydropyridine with Formaldehyde.—A procedure similar to that described for the preparation of 3-acetyl-1-methylpiperidine applied to 17.5 g. (0.126 mole) of 1,2-dimethyl-5-ethyl-Δ²-tetrahydropyridine gave 7.76 g. (23%) of **3-acetyl-5-ethyl-1-methylpiperidine**, b.p. 105° (18 mm.), $n^{21}D$ 1.4617, and 9.9 g. of higher-boiling material.

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.96; H, 11.32; N, 8.28. Found: C, 70.21; H, 11.42; N, 8.53.

The infrared spectrum (liquid film) had a strong maximum at 1710 cm.$^{-1}$.

The perchlorate crystallized from acetone–ether as colorless prisms, m.p. 141–142°.

Anal. Calcd. for $C_{10}H_{20}ClNO_5$: C, 44.53; H, 7.47; N, 5.20. Found: C, 44.60; H, 7.28; N, 5.19.

1,2,3-Trimethylpiperidine.—A modification of the procedure of Bradlow and Vanderwerf[54] for the potassium ferricyanide oxidation of β-picoline methosulfate in which isoamyl alcohol replaced benzene as the extraction solvent yielded 69% of **1,3-dimethyl-2-pyridone**, b.p. 80–82° (1 mm.), $n^{20}D$ 1.5548. Hydrogenation in glacial acetic acid using platinum oxide catalyst[55] afforded **1,3-dimethyl-2-piperidone** in 89% yield, b.p. 113–114° (18 mm.), $n^{20}D$ 1.4744.

Anal. Calcd. for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.01. Found: C, 65.70; H, 10.26; N, 11.06.

The reaction between 12.7 g. (0.10 mole) of 1,3-dimethyl-2-piperidone and 0.40 mole of methylmagnesium iodide yielded 10.3 g. (43%) of **1,2,3-trimethyl-Δ¹-tetrahydropyridinium perchlorate**, m.p. 225–226°, colorless needles from acetone–ether.

Anal. Calcd. for $C_8H_{16}ClNO_4$: C, 42.57; H, 7.15; N, 6.21. Found: C, 42.31; H, 7.26; N, 6.11.

The corresponding base, **1,2,3-trimethyl-Δ²-tetrahydropyridine**, had b.p. 63–64° (18 mm.), $n^{25}D$ 1.4817.

Anal. Calcd. for $C_8H_{15}N$: C, 76.74; H, 12.08; N, 11.19. Found: C, 76.80; H, 12.31; N, 11.13.

Hydrogenation of 8.6 g. (0.038 mole) of 1,2,3-trimethyl-Δ¹-tetrahydropyridinium perchlorate in 200 ml. of ethanol at 2–3 atmospheres using platinum oxide catalyst was followed by removal of the catalyst and solvent. The residue was taken up in water, basified and the mixture was extracted with ether. Isolation of the solute was followed by distillation from sodium to give 3.84 g. (80%) of **1,2,3-trimethylpiperidine**, b.p. 132°, $n^{20}D$ 1.4463. **The picrate** crystallized from ethanol as yellow plates, m.p. 224°.

Anal. Calcd. for $C_{14}H_{20}N_4O_7$: C, 47.19; H, 5.66; N, 15.72. Found: C, 47.22; H, 5.86; N, 15.90.

Mercuric Acetate Oxidation of 1,2,3-Trimethylpiperidine.—Oxidation of 1,2,3-trimethylpiperidine by the general procedure yielded 57% of 1,2,3-trimethyl-Δ¹-tetrahydropyridinium perchlorate, m.p. 223–225°, colorless needles from acetone–ether, identical with the sample described above.

1,3-Dimethyl-2-ethylpiperidine.—The reaction between 64 g. (0.50 mole) of 1,3-dimethyl-2-piperidone[54] and 2.0 moles of ethylmagnesium iodide gave 41.5 g. (32%) of **1,3-dimethyl-2-ethyl-Δ¹-tetrahydropyridinium perchlorate** and 32.5 g. (40%) of 2,2-diethyl-1,3-dimethylpiperidine. The former crystallized from acetone–ether as colorless prisms, m.p. 237–238.5°.

Anal. Calcd. for $C_9H_{18}ClNO_4$: C, 45.09; H, 7.57; N, 5.84. Found: C, 45.33; H, 7.47; N, 5.79.

The corresponding base, **1,3-dimethyl-2-ethyl-Δ²-tetrahydropyridine**, had b.p. 77° (18 mm.), $n^{24}D$ 1.4797.

Anal. Calcd. for $C_9H_{17}N$: C, 77.63; H, 12.31; N, 10.06. Found: C, 77.24; H, 12.40; N, 9.56.

The 2,2-diethyl-1,3-dimethylpiperidine was purified by distillation, b.p. 100–102° (20 mm.), $n^{23}D$ 1.4710.

Anal. Calcd. for $C_{11}H_{23}N$: C, 78.03; H, 13.69; N, 8.27. Found: C, 78.42; H, 13.88; N, 8.11.

2,2-Diethyl-1,3-dimethylpiperidine picrate crystallized from ethanol as yellow prisms, m.p. 220–222°.

Anal. Calcd. for $C_{17}H_{26}N_4O_7$: C, 51.25; H, 6.58; N, 14.06. Found: C, 51.33; H, 6.66; N, 13.78.

Hydrogenation of 8.5 g. (0.035 mole) of 1,3-dimethyl-2-ethyl-Δ¹-tetrahydropyridinium perchlorate using platinum oxide yielded 4.10 g. (80%) of **1,3-dimethyl-2-ethylpiperidine**, b.p. 160°, $n^{20}D$ 1.4523.

Anal. Calcd. for $C_9H_{19}N$: C, 76.52; H, 13.56; N, 9.92. Found: C, 76.48; H, 13.87; N, 9.52.

1,3-Dimethyl-2-ethylpiperidine picrate crystallized from ethanol as yellow plates, m.p. 180–181°.

Anal. Calcd. for $C_{15}H_{22}N_4O_7$: C, 48.64; H, 5.99; N, 15.13. Found: C, 48.96; H, 5.90; N, 15.29.

Mercuric Acetate Oxidation of 1,3-Dimethyl-2-ethylpiperidine.—The oxidation of 20 g. (0.142 mole) of 1,3-dimethyl-2-ethylpiperidine was carried out in the usual manner, and the products were isolated by fractional distillation of the residue remaining from the ether extracts. Conversion of the distillate fractions to perchlorate salts indicated that although the chief product was 1,3-dimethyl-2-ethyl-Δ²-tetrahydropyridine (identified as 1,3-dimethyl-2-ethyl-Δ¹-tetrahydropyridinium perchlorate, m.p. 237–238°), an appreciable amount of hydroxylated product was also obtained. The infrared spectrum of a Nujol mull of the perchlorate salt, m.p. 224–229° dec., from the higher-boiling fractions exhibited infrared absorption maxima at 1672(s) and 3440(m) cm.$^{-1}$, corresponding to $>C{=}\overset{+}{N}<$ and –OH functions, respectively. The total yield of bases was 13.9 g.

Mercuric Acetate Oxidation of 2-Benzyl-1,2,6-trimethylpiperidine.—Oxidation of 22 g. (0.10 mole) of 2-benzyl-1,2,6-trimethylpiperidine, obtained (see above) from the reaction of benzylmagnesium chloride with 1,2,6-trimethyl-Δ¹-tetrahydropyridinium perchlorate, with mercuric acetate yielded 21.6 g. (67%) of **6-benzyl-1,2,6-trimethyl-Δ¹-tetrahydropyridinium perchlorate**, m.p. 164–166°, colorless plates from ethanol.

Anal. Calcd. for $C_{15}H_{22}ClNO_4$: C, 57.04; H, 7.02; N, 4.44. Found: C, 57.23; H, 7.04; N, 4.25.

The corresponding **base** was obtained from the perchlorate in the usual manner, b.p. 173–174° (22 mm.), $n^{23}D$ 1.5487.

Anal. Calcd. for $C_{15}H_{21}N$: C, 83.66; H, 9.83; N, 6.51. Found: C, 83.24; H, 9.44; N, 6.31.

2,6-Dibenzyl-1,2,6-trimethylpiperidine.—The combination of 13 g. (0.041 mole) of 6-benzyl-1,2,6-trimethyl-Δ¹-tetrahydropyridinium perchlorate and the Grignard reagent from 18.0 g. (0.142 mole) of benzyl chloride and 4.0 g. (0.164 gram atom) of magnesium produced 12 g. (95%) of 2,6-dibenzyl-1,2,6-trimethylpiperidine, b.p. 160–162° (0.2 mm.), $n^{23}D$ 1.5700.

Anal. Calcd. for $C_{22}H_{29}N$: C, 85.94; H, 9.51; N, 4.56. Found: C, 85.87; H, 9.69; N, 4.49.

The perchlorate crystallized from ethanol as colorless prisms, m.p. 243°.

Anal. Calcd. for $C_{22}H_{30}ClNO_4$: C, 64.78; H, 7.41; N, 3.43. Found: C, 64.54; H, 7.46; N, 3.31.

(54) H. L. Bradlow and C. A. Vanderwerf, *J. Org. Chem.*, **16**, 73 (1951).

(55) N. J. Leonard and E. Barthel, Jr., THIS JOURNAL, **71**, 3098 (1949).

Although some mercurous acetate was precipitated during attempted oxidation of 2,6-dibenzyl-1,2,6-trimethylpiperidine by mercuric acetate, no pure product could be isolated uncontaminated with starting material.

1,2,2,6,6-Pentamethylpiperidine.—A mixture of 5.87 g. (0.0424 mole) of 2,2,6,6-tetramethylpiperidine[56] and 15 g. of potassium carbonate in 50 ml. of ethanol was cooled in ice and stirred vigorously while 6.0 g. (0.024 mole) of methyl iodide in 50 ml. of ethanol was added dropwise. The mixture was diluted with about 20 ml. of ether and warmed gently under reflux overnight with stirring. Most of the ethanol was distilled, and the cooled residue was treated with ether. The ethereal mixture was filtered, and the solids were washed on the filter with several portions of ether. The combined clear filtrates were acidified with dry hydrogen chloride and evaporated. The residue was dissolved in water, basified with sodium hydroxide and treated with 20 g. of benzenesulfonyl chloride. Reaction was completed by heating the mixture on the steam-bath for a short time. The product was steam distilled and extracted from the distillate with ether. Distillation of the dried extracts from sodium gave 3.8 g. (59%) of 1,2,2,6,6-pentamethylpiperidine, b.p. 147°, $n^{21}D$ 1.4550.

Anal. Calcd. for $C_{10}H_{21}N$: C, 77.33; H, 13.63; N, 9.02. Found: C, 76.85; H, 13.24; N, 9.23.

The picrate crystallized from ethanol as yellow plates, m.p. 275° dec.

Anal. Calcd. for $C_{16}H_{24}N_4O_7$: C, 49.99; H, 6.29; N, 14.58. Found: C, 50.23; H, 6.58; N, 14.27.

No mercurous acetate was precipitated during the attempted mercuric acetate oxidation of 1,2,2,6,6-pentamethylpiperidine, and the starting material was isolated following the reaction conditions described in the general procedure. Interesting by comparison is the fact that the unsubstituted nucleus, piperidine, gave no evidence of reaction (no colored complex, no mercurous acetate precipitate, 64% of piperidine recovered) with mercuric acetate under the general procedure conditions. The same was true for pyrrolidine.

Mercuric Acetate Oxidation of 1-Methylpiperidine. 1,1'-Dimethyl-Δ^2-tetrahydroanabasine.—Oxidation of 20.0 g. (0.20 mole) of 1-methylpiperidine[36] was carried out in the usual way. The dried ether extracts were distilled to yield, after a small forerun of unreacted starting material, 13.3 g. (67%) of crude 1,1'-dimethyl-Δ^2-tetrahydroanabasine, b.p. 143–144° (22 mm.), colorless when redistilled, b.p. 128–129° (18 mm.), $n^{22}D$ 1.5068.

Anal. Calcd. for $C_{12}H_{22}N_2$: C, 74.17; H, 11.41; N, 14.42. Found: C, 74.09; H, 11.35; N, 14.26.

The infrared spectrum of a liquid film had a strong maximum at 1667 cm.$^{-1}$ and no bands characteristic of an –NH– group. A similar spectrum was obtained from a 5% solution in carbon tetrachloride, and a 5% solution in chloroform had a strong maximum at 1660 cm.$^{-1}$ and an additional medium band at 2480 cm.$^{-1}$. In ether solution, the compound had no ultraviolet absorption maximum above 217 mμ, but in ethanol solution appreciable absorption at 235 mμ developed.

The nature of the diperchlorate salt showed a marked dependence upon the method of preparation, and no uniform product was obtained. Even so, the infrared spectra of the crude perchlorate preparations gave some information relevant to the structure of the parent amine. Prepared from the amine in ethanol–ether by the dropwise addition of perchloric acid, the perchlorate was obtained as a thick oil which could not be crystallized but which had an analysis suggestive of a diperchlorate.

Anal. Calcd. for $C_{12}H_{24}Cl_2N_2O_8$: C, 36.46; H, 6.12; N, 7.09. Found: C, 35.51; H, 6.04; N, 6.88.

The infrared spectrum of a liquid film exhibited a wide band in the 3100–3200 cm.$^{-1}$ region and maxima at 2200, 2020, 1700(w), 1662 and 1605 cm.$^{-1}$. Rapid addition of the free base to excess perchloric acid in ethanol–ether solution with vigorous stirring produced a colorless crystalline solid which became oily on standing. The infrared spectrum was similar to that of the crude material mentioned above, except that the 1700 cm.$^{-1}$ band was more intense.

The monopicrate was prepared in ethanol and washed with anhydrous ether, crude m.p. 131°. Attempts to purify the material resulted in a depression of melting point. The infrared spectrum of a Nujol mull exhibited maxima (selected) at 3540, 2740 and 1650 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{25}N_5O_7$: C, 51.06; H, 5.95; N, 16.54. Found: C, 50.63; H, 5.99; N, 15.86.

Hydrogenations of 1,1'-Dimethyl-Δ^2-tetrahydroanabasine. a. In Glacial Acetic Acid with Platinum Oxide.—The reduction of 0.19 g. (1.01 mmoles) of 1,1'-dimethyl-Δ^2-tetrahydroanabasine in 25 ml. of glacial acetic acid using 50 mg. of platinum oxide consumed 41.8 ml. (S.T.P.) (1.87 mmoles) of hydrogen, or 1.85 mmoles of hydrogen/mmole of amine. No inflection point was observed in the hydrogenation curve. A larger run in which 20 g. (0.20 mole) of 1-methylpiperidine was oxidized in the usual way and the crude product reduced directly without distillation yielded 11.8 g. (60%) of **1-methyl-3-(5'-methylaminopentyl)-piperidine**, b.p. 147–148° (18 mm.), $n^{24}D$ 1.4675.

Anal. Calcd. for $C_{12}H_{26}N_2$: C, 72.66; H, 13.21; N, 14.12. Found: C, 72.47; H, 13.08; N, 14.00.

Another sample of this compound was prepared by the method of Lukeš and Kovář[25] for direct comparison. The sodium–butanol reduction of 22 g. (0.195 mole) of 1-methyl-2-piperidone yielded a very small quantity of tertiary amines, 10.5 g. (15%) of the *p*-toluenesulfonyl derivative of 1-methyl-3-(5'-methylaminopentyl)-piperidine and a considerable non-distillable residue. The free base was obtained from the *p*-toluenesulfonamide in poor yield by reaction with lithium aluminum hydride,[25] b.p. 136–138° (11 mm.), $n^{27}D$ 1.4650. Infrared spectra of liquid films of the two samples were identical, with a band of medium intensity at 3270 cm.$^{-1}$ and no maxima in the 1600–1700 cm.$^{-1}$ region.

The dipicrate separated from ethanol as yellow prisms, m.p. 139–141° (reported[25,57] 136–137°).

Anal. Calcd. for $C_{24}H_{32}N_8O_{14}$: C, 43.90; H, 4.91; N, 17.07. Found: C, 44.16; H, 4.57; N, 16.99.

The dihydrochloride separated from acetone–ethanol–ether as colorless prisms, m.p. 209–210° (reported[25] 201–202°).

Anal. Calcd. for $C_{12}H_{28}Cl_2N_2$: C, 53.12; H, 10.40; N, 10.33. Found: C, 52.86; H, 10.38; N, 10.08.

The free base recovered from the dihydrochloride salt was identical with the samples of 1-methyl-3-(5'-methylaminopentyl)-piperidine described above.

The benzoyl derivative was a very light yellow oil, b.p. 210° (0.5 mm.), $n^{20}D$ 1.5250.

Anal. Calcd. for $C_{19}H_{30}N_2O$: C, 75.44; H, 10.01; N, 9.27. Found: C, 75.24; H, 9.77; N, 9.26.

1-Methyl-3-(5'-dimethylaminopentyl)-piperidine dimethiodide was prepared by treating 1-methyl-3-(5'-methylaminopentyl)-piperidine with excess methyl iodide. Several recrystallizations from ethanol–acetone–ether gave colorless prisms, m.p. 253–254°.

Anal. Calcd. for $C_{15}H_{34}I_2N_2$: C, 36.30; H, 6.90; N, 5.64. Found: C, 35.96; H, 6.93; N, 5.45.

1-Methyl-3-(5'-dimethylaminopentyl)-piperidine was prepared by methylation of 1-methyl-3-(5'-methylaminopentyl)-piperidine with 20 ml. of 98% formic acid and 12 ml. of 37% formalin by the usual procedure, b.p. 144–145° (18 mm.), $n^{20}D$ 1.4628, yield 3.9 g. (82%).

Anal. Calcd. for $C_{13}H_{28}N_2$: C, 73.51; H, 13.29; N, 13.20. Found: C, 72.85; H, 13.29; N, 12.85.

The dipicrate separated from ethanol as yellow prisms, m.p. 131–134°.

Anal. Calcd. for $C_{25}H_{34}N_8O_{14}$: C, 44.77; H, 5.11; N, 16.71. Found: C, 44.98; H, 5.20; N, 16.42.

The dimethiodide, m.p. 251–253°, was identical by the usual criteria with the sample obtained by the action of excess methyl iodide on 1-methyl-3-(5'-methylaminopentyl)-piperidine.

1-Methyl-3-[5'-(methylacetamido)-pentyl]-piperidine was obtained by the action of acetyl chloride on 9.5 g. (0.048 mole) of 1-methyl-3-(5'-methylaminopentyl)-piperidine as a very light yellow oil, b.p. 128–129° (0.2 mm.), $n^{22}D$

(56) N. J. Leonard and E. W. Nommensen, THIS JOURNAL, **71**, 2808 (1949).

(57) R. Lukeš and J. Kovar, *Coll. Czech. Chem. Commun.*, **20**, 1004 (1955).

1.4832, yield 10.7 g. (93%), infrared absorption maximum (liquid film) at 1650(s) cm.$^{-1}$ (amide C=O).

Anal. Calcd. for $C_{14}H_{28}N_2O$: C, 69.95; H, 11.74; N, 11.65. Found: C, 70.19; H, 11.71; N, 11.87.

1-Methyl-3-(5′-ethylmethylaminopentyl)-piperidine was obtained by reduction of 7.95 g. (0.033 mole) of the acetyl derivative described above with excess lithium aluminum hydride, b.p. 161° (20 mm.), $n^{22}D$ 1.4650, yield 6.50 g. (87%).

Anal. Calcd. for $C_{14}H_{30}N_2$: C, 74.27; H, 13.36; N, 12.37. Found: C, 74.64; H, 13.23; N, 11.58.

The dipicrate crystallized from water as yellow prisms, m.p. 123–125°.

Anal. Calcd. for $C_{26}H_{36}N_8O_{14}$: C, 45.61; H, 5.30; N, 16.36. Found: C, 45.32; H, 5.16; N, 16.15.

b. Hydrogenation of XVII in Ethanol with Raney Nickel.—The hydrogenation of 1,1′-dimethyl-Δ^2-tetrahydroanabasine in 25 ml. of ethanol with W-2 Raney nickel consumed two mmoles of hydrogen/mmole of amine.

c. Hydrogenation of XVII in Strong Acid with Platinum Oxide.[30]—The uptake of hydrogen by 0.580 g. (3.01 mmoles) of 1,1′-dimethyl-Δ^2-tetrahydroanabasine in 1:1 ethanol–12 *N* hydrochloric acid with 50 mg. of platinum oxide was 112.7 ml. (S.T.P.) (5.03 mmoles), or 1.68 mmoles of hydrogen/mmole of amine. No inflection point in the hydrogenation curve at 1 mmole was noted. A larger run was carried out in which 11.0 g. (0.057 mole) of amine was reduced under these conditions, and the products were separated by converting the secondary amine components to their *p*-toluenesulfonamides and steam distilling the tertiary amine components. There was thus obtained 4.70 g. (24%) of the *p*-toluenesulfonyl derivative of 1-methyl-3-(5′-methylaminopentyl)-piperidine, b.p. 214–217° (0.3 mm.), $n^{23}D$ 1.5222 (reported[25] 214–217° (1.2 mm.)). Redistillation of the tertiary amines from sodium gave 6.83 g. (61%) of **1,1′-dimethyl-2,3′-bipiperidine**, b.p. 138° (18 mm.), $n^{22}D$ 1.4913 (reported[25] 122–123° (10 mm.), $n^{15}D$ 1.4948); **dipicrate**, yellow prisms, m.p. 209–210° (reported[25] 203–204°). The base showed no infrared absorption in the –NH– region.

Other **Reactions of 1,1′-Dimethyl-Δ^2-tetrahydroanabasine.** **a. Condensation with Methyl Acetoacetate.**—A solution of 4.0 g. (0.02 mole) of 1,1′-dimethyl-Δ^2-tetrahydroanabasine and 25 g. of distilled methyl acetoacetate in 100 ml. of 50% aqueous methanol was allowed to stand at about 25° for 3 days. Excess 12 *N* hydrochloric acid was added, and the resulting solution was heated on the steam-bath for several hours. The ethanol was removed in vacuum, and the aqueous residue was washed with ether to remove non-basic material. The aqueous layer was basified with potassium carbonate and was extracted with ether. The combined basic ether extracts were dried and concentrated, and the residue was fractionally distilled to give 3.6 g. (58%) of **N-methylisopelletierine**, b.p. 97–99° (18 mm.), $n^{22}D$ 1.4703 (reported[31] 110–120° at aspirator pressure), infrared maximum (liquid film) 1710 cm.$^{-1}$; **picrate**, yellow prisms from ethanol, m.p. 154–156° (reported[25] 155–156°); **semicarbazone hydrochloride**, colorless prisms from methanol, m.p. 200–201° dec. (reported[25] 204–205°). Essentially the same results were obtained by using the crude reaction product from the mercuric acetate oxidation of 1-methylpiperidine, following removal of mercurous and mercuric salts and basification with potassium carbonate. The extended reaction time under basic conditions was apparently essential. Short periods of combination of the unsaturated amine and methyl acetoacetate were ineffective, as was the inclusion of methyl acetoacetate in the original oxidizing mixture of methylpiperidine.

b. Metal Hydride Reduction.—From an attempt to reduce 1,1′-dimethyl-Δ^2-tetrahydroanabasine with excess lithium aluminum hydride in anhydrous ether, the starting material was recovered nearly quantitatively. An attempt to reduce the semi-solid perchlorate from 1,1′-dimethyl-Δ^2-tetrahydroanabasine in ether suspension with excess lithium aluminum hydride gave a mixture of bases, b.p. 130–143° (18 mm.), $n^{26}D$ 1.4953–1.4820, infrared maxima at 1660(s) and at 3100–3400 cm.$^{-1}$ (broad). The results with borohydride were unusual but more rewarding. A solution of 3.0 g. (0.016 mole) of 1,1′-dimethyl-Δ^2-tetrahydroanabasine in 100 ml. of 50% aqueous methanol was treated with 6.0 g. (0.16 mole) of sodium borohydride in small portions with vigorous stirring. The solution was heated under reflux for 1.5 hr. and allowed to stand at 25° overnight. Excess hydrochloric acid was added, and most of the alcohol was removed in vacuum. The aqueous residue was washed with ether (discarding the washings), basified with potassium carbonate and extracted with several portions of ether. The combined dried extracts were distilled, yielding 2.6 g. of bases, b.p. 138–139° (18 mm.), $n^{21}D$ 1.4877, infrared maximum (liquid film) indicative of an –NH– group and a weak broad band at 1675 cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{24}N_2$: C, 73.41; H, 12.32; N, 14.27. Found: C, 72.96; H, 12.26; N, 14.16.

The dipicrate of the unsaturated tert.,sec.,-amine constituent tentatively assigned the structure 1-methyl-3-(5′-methylamino-1′-pentenyl)-piperidine separated from water in yellow prisms, m.p. 224–225°.

Anal. Calcd. for $C_{24}H_{30}N_8O_{14}$: C, 44.04; H, 4.62; N, 17.12. Found: C, 44.45; H, 4.67; N, 16.83.

Reaction with **benzenesulfonyl chloride** under the usual conditions for the separation of sec.- and tert.-amines yielded a small amount of **1,1′-dimethyl-2,3′-bipiperidine**, b.p. 55° (0.2 mm.), $n^{25}D$ 1.4896, and **the N′-benzenesulfonyl derivative of 1-methyl-3-(5′-methylamino-1′-pentenyl)-piperidine** (tentative), b.p. 214° (0.3 mm.).

Anal. Calcd. for $C_{18}H_{28}N_2O_2S$: C, 64.26; H, 8.39; N, 8.33. Found: C, 64.77; H, 8.77; N, 8.30.

The catalytic hydrogenation of 0.226 g. of the amine obtained initially from the borohydride reduction resulted in the absorption of 22.7 ml. (S.T.P.) of hydrogen, or 0.88 mmole per mmole of $C_{12}H_{24}N_2$ base.

c. Miscellaneous Attempted Reactions.—The following reagents with 1,1′-dimethyl-Δ^2-tetrahydroanabasine gave inconclusive results in the form of unidentified products or impractical mixtures: formaldehyde and dimethylamine, formic acid, potassium ferricyanide in dilute alkali. Reaction of the oily perchlorate with aqueous potassium cyanide gave a diaminonitrile contaminated with starting material. Reduction of the diaminonitrile with lithium aluminum hydride gave a triamine which was still contaminated with the original material.

Mercuric Acetate Oxidation of 1-Benzylpiperidine.—Oxidation of 18.1 g. (0.10 mole) of 1-benzylpiperidine[36] with mercuric acetate yielded 6.97 g. (39%) of **1,1′-dibenzyl-Δ^2-tetrahydroanabasine**, b.p. 153–155° (0.3 mm.), $n^{28}D$ 1.5728, infrared maximum at 1662 cm.$^{-1}$. No benzaldehyde was detected in the reaction mixture.

Anal. Calcd. for $C_{24}H_{30}N_2$: C, 83.19; H, 8.73. Found: C, 83.45; H, 8.61.

Mercuric Acetate Oxidation of 1-Cyclohexylpiperidine, 1-Cyclopentylpiperidine and 1-Cyclohexylpyrrolidine.—The crude "dimeric" product from 1-cyclohexylpiperidine had b.p. 182–185° (0.3 mm.), $n^{21}D$ 1.5285, infrared maxima (liquid film) at 1659, 1640, ~1627 cm.$^{-1}$; from 1-cyclopentylpiperidine, b.p. 180–185° (0.2 mm.), $n^{26}D$ 1.5180, infrared maxima at 1730, 1638, 3010(m) cm.$^{-1}$ (also piperidine (18%)); from 1-cyclohexylpyrrolidine, could not be characterized.

Mercuric Acetate Oxidation of 1,3-Dimethylpiperidine.—Oxidation of 11.3 g. (0.10 mole) of 1,3-dimethylpiperidine yielded, on distillation, 4 g. of a mixture of starting material and monomeric enamines and 7 g. of crude dimeric product. The infrared spectrum of the low-boiling fraction, b.p. 155–165°, $n^{22}D$ 1.4710, exhibited two poorly resolved maxima at 1673 and 1648 cm.$^{-1}$. Authentic **1,3-dimethyl-Δ^2-tetrahydropyridine** prepared by the sodium–butanol reduction of 1,3-dimethyl-2-piperidone[17] exhibited a strong maximum at 1673 cm.$^{-1}$. The 1648 cm.$^{-1}$ maximum in the spectrum of the mixture may be due to the presence of **1,5-dimethyl-Δ^2-tetrahydropyridine**, since this maximum is due neither to the 1,3-isomer nor to the "dimeric" product.

The high boiling fraction had b.p. 76° (0.3 mm.), $n^{24}D$ 1.4987, infrared maximum at 1667 cm.$^{-1}$ (infrared spectrum in general similar to that of 1,1′-dimethyl-Δ^2-tetrahydroanabasine).

Anal. Calcd. for $C_{14}H_{26}N_2$: C, 75.61; H, 11.79; N, 12.60. Found: C, 75.44; H, 11.69; N, 12.46.

3,5-Diethyl-1-methylpiperidine.—A mixture of 3,5-diethyl-1-methyl-4-piperidone,[18] b.p. 99–100° (18 mm.), $n^{26}D$ 1.4654, 35 ml. of 100% hydrazine hydrate and 50 g. of potassium hydroxide in 70 ml. of triethylene glycol even-

tually yielded 6.72 g. (74%) of 3,5-diethyl-1-methylpiperidine, b.p. 167–168°, $n^{24}D$ 1.4483.

Anal. Calcd. for $C_{10}H_{21}N$: C, 77.33; H, 13.63; N, 9.02. Found: C, 76.27; H, 13.56; N, 9.05.

The picrate separated from aqueous ethanol as yellow prisms, m.p. 101–103°.

Anal. Calcd. for $C_{16}H_{24}N_4O_7$: C, 49.99; H, 6.29; N, 14.58. Found: C, 50.26; H, 6.27; N, 14.29.

Mercuric Acetate Oxidation of 3,5-Diethyl-1-methylpiperidine.—Oxidation of 16 g. (0.10 mole) of 3,5-diethyl-1-methylpiperidine by the general procedure yielded 16 g. (61%) of **3,5-diethyl-1-methyl-Δ^1-tetrahydropyridinium perchlorate**, colorless prisms from ethanol, m.p. 160–162°, infrared maximum at 1700 cm.$^{-1}$ (Nujol mull).

Anal. Calcd. for $C_{10}H_{20}ClNO_4$: C, 47.34; H, 7.95; N, 5.52. Found: C, 47.54; H, 7.97; N, 5.50.

3,5-Diethyl-1-methyl-Δ^2-tetrahydropyridine was liberated from the perchlorate in the usual manner, b.p. 85–86° (18 mm.), $n^{20}D$ 1.4706, infrared maximum at 1666 cm.$^{-1}$ (liquid film), 1667 cm.$^{-1}$ (in pyrrolidine).

Anal. Calcd. for $C_{10}H_{19}N$: C, 78.36; H, 12.50. Found: C, 77.66; H, 11.81.

Reaction of Benzylmagnesium Chloride with 3,5-Diethyl-1-methyl-Δ^1-tetrahydropyridinium Perchlorate.—Reaction of the Grignard reagent from 8.0 g. (0.063 mole) of benzyl chloride and 2.0 g. (0.082 g. atom) of magnesium with 4.0 g. (0.016 mole) of 3,5-diethyl-1-methyl-Δ^1-tetrahydropyridinium perchlorate by the usual procedure yielded 2.62 g. (69%) of **2-benzyl-3,5-diethyl-1-methylpiperidine**, b.p. 173–174° (18 mm.), $n^{22}D$ 1.5142.

Anal. Calcd. for $C_{17}H_{27}N$: C, 83.20; H, 11.09; N, 5.70. Found: C, 82.97; H, 10.99; N, 5.95.

The hydrochloride separated from acetone–ether as colorless prisms, m.p. 203–204°.

Anal. Calcd. for $C_{17}H_{28}ClN$: C, 72.43; H, 10.01; N, 4.97. Found: C, 72.55; H, 10.53; N, 5.02.

The infrared spectrum (Nujol mull) indicated that no ring fission had occurred (no maxima due to $-\overset{+}{N}H_2-$).

Reaction of Potassium Cyanide with 3,5-Diethyl-1-methyl-Δ^1-tetrahydropyridinium Perchlorate.—The general procedure applied to the treatment of 6.0 g. (0.025 mole) of 3,5-diethyl-1-methyl-Δ^1-tetrahydropyridinium perchlorate with excess potassium cyanide yielded 4.0 g. (93%) of **2-cyano-3,5-diethyl-1-methylpiperidine**, b.p. 119–120° (18 mm.), $n^{22}D$ 1.4612, infrared maximum at 2225 cm.$^{-1}$ (none in 6 μ region).

Anal. Calcd. for $C_{11}H_{20}N_2$: C, 73.28; H, 11.18; N, 15.54. Found: C, 73.08; H, 11.15; N, 15.44.

Reduction of this compound with excess lithium aluminum hydride under the usual conditions yielded 96% of **2-aminomethyl-3,5-diethyl-1-methylpiperidine**, b.p. 138–139° (20 mm.), $n^{21}D$ 1.4743.

Anal. Calcd. for $C_{11}H_{24}N_2$: C, 71.68; H, 13.13; N, 15.20. Found: C, 71.53; H, 13.08; N, 14.98.

The infrared spectrum (liquid film) exhibited maxima at 3280(m), 3350(m), 1600 (broad), 900–750 cm.$^{-1}$ (broad). Nitrile and enamine bands were absent.

The monopicrate separated from water as yellow prisms, m.p. 162°.

Anal. Calcd. for $C_{17}H_{27}N_5O_7$: C, 49.38; H, 6.58; N, 16.94. Found: C, 49.76; H, 6.60; N, 16.96.

Mercuric Acetate Oxidation of 2,2-Diethyl-1-methylpiperidine.—Oxidation of 2,2-diethyl-1-methylpiperidine in the usual way gave a colorless liquid, b.p. 175–180° (18 mm.), $n^{21}D$ 1.4938, tentatively assigned the structure 1,1′-dimethyl-6,6,6′,6′-tetraethyl-Δ^2-tetrahydroanabasine by analogy with other "dimeric" products.

1,3,3-Trimethylpiperidine.—Methylation of 22.5 g. (0.20 mole) of 3,3-dimethylpiperidine, prepared by the method of Schreyer,[58] with 125 g. of formic acid and 85 g. of 37% formalin furnished 22.5 g. (89%) of 1,3,3-trimethylpiperidine, b.p. 134°, $n^{20}D$ 1.4372.

Anal. Calcd. for $C_8H_{17}N$: C, 75.52; H, 13.47; N, 11.01. Found: C, 75.44; H, 13.35; N, 10.83.

The picrate separated from dilute ethanol as yellow plates, m.p. 192–193°.

Anal. Calcd. for $C_{14}H_{20}N_4O_7$: C, 47.19; H, 5.66; N, 15.73. Found: C, 47.33; H, 5.86; N, 15.57.

The perchlorate crystallized from methanol–ether as colorless prisms, m.p. 135–136°.

Anal. Calcd. for $C_8H_{18}ClNO_4$: C, 42.20; H, 7.92; N, 6.15. Found: C, 42.33; H, 8.01; N, 6.01.

Mercuric Acetate Oxidation of 1,3,3-Trimethylpiperidine.—The oxidation of 12.7 g. (0.10 mole) of 1,3,3-trimethylpiperidine with mercuric acetate followed the general procedure, except that after removal of mercuric sulfide the aqueous filtrate was extracted with several portions of chloroform. Distillation of these extracts yielded 2.0 g. (15%) of crude **1,3,3-trimethyl-2-piperidone**, redistilled at 106–107° (18 mm.) (slight odor of sulfur-containing material), $n^{21}D$ 1.4712, infrared maximum 1640 cm.$^{-1}$.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 67.19; H, 10.65; N, 9.58.

The aqueous residue was then basified under ether with potassium carbonate and extracted with several portions of ether. The dried extracts, on treatment with perchloric acid solution, yielded 14 g. of colorless powder, m.p. 117–122°, which darkened on standing. Several recrystallizations of a portion of this material from acetone–ether gave **1,5,5-trimethyl-Δ^1-tetrahydropyridinium perchlorate**, m.p. 162–163°, infrared maximum (Nujol) 1697 cm.$^{-1}$.

Anal. Calcd. for $C_8H_{16}ClNO_4$: C, 42.57; H, 7.15; N, 6.21. Found: C, 43.03; H, 6.74; N, 5.99.

The remaining crude perchlorate salt was basified, and the dried ether extracts were distilled to give 8.5 g. total of bases. The infrared spectrum (liquid film) of a sample of the lower boiling components, b.p. 158–165°, suggested that it was a mixture of 1,3,3-trimethylpiperidine and **1,5,5-trimethyl-Δ^2-tetrahydropyridine** (infrared maximum 1652(m) cm.$^{-1}$). A redistillation of the higher boiling component yielded a portion, b.p. 78° (0.3 mm.), $n^{22}D$ 1.4938, assigned the structure 1,1′,5,5,5′,5′-hexamethyl-Δ^2-tetrahydroanabasine, b.p. 78° (0.3 mm.), $n^{22}D$ 1.4938, infrared maximum 1664 cm.$^{-1}$ (s) (a weak maximum at 1713 cm.$^{-1}$ suggested a contaminant).

Anal. Calcd. for $C_{16}H_{30}N_2$: C, 76.74; H, 12.08; N, 11.19. Found: C, 76.97; H, 11.80; N, 10.85.

1,4,4-Trimethylpiperidine.—β,β-Dimethylglutaric anhydride prepared[59] from 80 g. (0.50 mole) of β,β-dimethylglutaric acid was heated at 120–140° in an oil-bath while dry methylamine was passed through the melt during 0.5 hr. The mixture was maintained at 200–210° for 3 hr. and then distilled, b.p. 131° (18 mm.), m.p. 61–63°, yield 60 g. (72%) of **N,β,β-trimethylglutarimide.**

Anal. Calcd. for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 62.13; H, 8.60; N, 8.98.

A solution of 40 g. (0.26 mole) of the imide in 500 ml. of anhydrous ether was added slowly to a slurry of a large excess of lithium aluminum hydride in ether. When the addition was complete, the mixture was stirred under reflux overnight. The usual isolation procedure employed to recover amines from hydride reductions yielded 28.8 g. (88%) of 1,4,4-trimethylpiperidine, b.p. 141–142°, $n^{22}D$ 1.4354.

Anal. Calcd. for $C_8H_{17}N$: C, 75.52; H, 13.47; N, 11.01. Found: C, 75.44; H, 13.67; N, 10.93.

The picrate separated from ethanol as yellow prisms, m.p. 231–232°.

Anal. Calcd. for $C_{14}H_{20}N_4O_7$: C, 47.19; H, 5.66; N, 15.73. Found: C, 47.41; H, 5.61; N, 15.53.

The perchlorate crystallized from acetone–ether as colorless prisms, m.p. 151–152°.

Anal. Calcd. for $C_8H_{18}ClNO_4$: C, 42.20; H, 7.92; N, 6.15. Found: C, 42.41; H, 7.92; N, 5.99.

Mercuric Acetate Oxidation of 1,4,4-Trimethylpiperidine.—The oxidation of 12.7 g. (0.10 mole) of 1,4,4-trimethylpiperidine followed the general procedure. Distillation of the dried ether extracts yielded 10.0 g. (79%) of crude monomeric unsaturated amine and 0.4 g. (3%) of "dimeric" product (infrared maxima at 1649(s) and 1678(m) cm.$^{-1}$). Redistillation of the monomer gave **1,4,4-trimethyl-Δ^2-tetrahydropyridine**, b.p. 132°, $n^{23}D$ 1.4533, infrared maxima at 3015(w) and 1645(s) cm.$^{-1}$.

(58) R. C. Schreyer, THIS JOURNAL, **74**, 3194 (1952).

(59) W. W. Crouch and H. L. Lochte, *ibid.*, **65**, 270 (1943).

Anal. Calcd. for $C_8H_{15}N$: C, 76.74; H, 12.08; N, 11.19. Found: C, 76.26; H, 12.22; N, 11.00.

1,4,4-Trimethyl-Δ^1-tetrahydropyridinium perchlorate formed from the base above in ethanol–ether was recrystallized from acetone–ether, colorless prisms, m.p. 88–89°.

Anal. Calcd. for $C_8H_{16}ClNO_4$: C, 42.57; H, 7.15; N, 6.21. Found: C, 42.70; H, 7.37; N, 5.99.

1,4,4-Trimethyl-Δ^1-tetrahydropyridinium picrate crystallized from aqueous ethanol as yellow prisms, m.p. 180° with decomposition (unsharp), infrared maximum (mull) at 1700 cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{18}N_4O_7$: C, 47.45; H, 5.12; N, 15.81. Found: C, 47.35; H, 5.25; N, 15.82.

2-Cyano-1,4,4-trimethylpiperidine.—The crude perchlorate salt from 4.5 g. (0.036 mole) of free base in water was treated with excess potassium cyanide following the usual procedure to give 4.6 g. (85%) of 2-cyano-1,4,4-trimethylpiperidine, b.p. 103° (18 mm.), $n^{25}D$ 1.4557, infrared maxima at 2220 and 2240 cm.$^{-1}$ (mull).

Anal. Calcd. for $C_9H_{16}N_2$: C, 71.01; H, 10.60; N, 18.40. Found: C, 70.84; H, 10.89; N, 18.32.

Reduction of this compound with excess lithium aluminum hydride yielded 87% of **2-aminomethyl-1,4,4-trimethylpiperidine**, b.p. 99° (18 mm.), $n^{24}D$ 1.4693.

Anal. Calcd. for $C_9H_{20}N_2$: C, 69.17; H, 12.90; N, 17.93. Found: C, 68.84; H, 12.94; N, 17.42.

The dipicrate crystallized from aqueous ethanol as yellow prisms, m.p. 196–197° dec.

Anal. Calcd. for $C_{21}H_{26}N_8O_{14}$: C, 41.04; H, 4.26; N, 18.24. Found: C, 41.26; H, 4.37; N, 18.29.

1-Ethyl-4-methylpiperidine.—Hydrogenation of 75 g. (0.81 mole) of pure γ-picoline in 200 ml. of ethanol at 200° and 150 atmospheres using Raney nickel W-2 catalyst yielded 78 g. (76%) of 1-ethyl-4-methylpiperidine, b.p. 147°, $n^{24}D$ 1.4373.

Anal. Calcd. for $C_8H_{17}N$: C, 75.52; H, 13.47; N, 11.01. Found: C, 75.14; H, 13.50; N, 10.87.

The picrate crystallized from dilute ethanol as yellow needles, m.p. 155–156°.

Anal. Calcd. for $C_{14}H_{20}N_4O_7$: C, 47.19; H, 5.66; N, 15.73. Found: C, 47.32; H, 5.69; N, 15.55.

Mercuric Acetate Oxidation of 1-Ethyl-4-methylpiperidine.—The usual oxidation procedure yielded about 80% of a mixture of monomeric enamine and "dimeric" product. Redistilled **1-ethyl-4-methyl-Δ^2-tetrahydropyridine** boiled at 54–55° (18 mm.), $n^{24}D$ 1.4604, infrared maxima at 3020 and 1640 cm.$^{-1}$. The perchlorate salt was an oil.

Anal. Calcd. for $C_8H_{15}N$: C, 76.74; H, 12.08; N, 11.19. Found: C, 76.06; H, 12.58; N, 11.11.

Redistilled **1,1'-diethyl-4,4'-dimethyl-Δ^2-tetrahydroanabasine** boiled at 162° (18 mm.), $n^{25}D$ 1.4985, infrared maximum at 1650 cm.$^{-1}$, oily perchlorate.

Anal. Calcd. for $C_{16}H_{30}N_2$: C, 76.74; H, 12.08; N, 11.19. Found: C, 76.93; H, 12.31; N, 11.21.

URBANA, ILLINOIS

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Terpenoids. XXXI.[1] The Structure and Stereochemistry of Medicagenic Acid[2]

BY CARL DJERASSI,[3] D. B. THOMAS,[3] A. L. LIVINGSTON[4] AND C. RAY THOMPSON[4]

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Medicagenic acid, a triterpenoid dihydroxy dicarboxylic acid from alfalfa, has been shown to be 2β,3β-dihydroxy-Δ^{12}-oleanene-23,28-dioic acid (Ia) by various degradations and by a direct correlation with arjunolic acid (VI). Quantitative lead tetraacetate oxidations have demonstrated that the glycol grouping in the related triterpenes asiatic acid, arjunolic acid, terminolic acid, barringtogenic acid and barringtogenol has the 2α,3β-orientation.

An examination[5] of the saponins of alfalfa (*Medicago sativa*) has led to the isolation of a new sapogenin, $C_{30}H_{46}O_6$, which was characterized as a dihydroxy dicarboxylic acid. The structure elucidation of this sapogenin—now named medicagenic acid—seemed particularly pertinent since the mixture of saponins which occurs in alfalfa is known to produce deleterious effects in chicks and ruminants[6] and since dicarboxylic acids of the pentacyclic triterpene series are very rare.[7] The present paper describes the establishment of the structure and stereochemistry of medicagenic acid.

Initial purification was accomplished *via* the diacetate Ib which was then methylated with diazomethane and chromatographed, since diacetoxy dimethyl medicagenate (Ic) lent itself particularly well to such purification and also crystallized readily.[8] Saponification of the diacetoxy dimethyl ester Ic with 5% potassium hydroxide or even with potassium carbonate solution led to the crystalline dimethyl medicagenate (Id).[9] Since the latter conditions are usually insufficient[10] to saponify the conventional 3β-acetoxy group of pentacyclic triterpenes, assumed to exist also in medicagenic acid, this indicated the presence of additional, activating substituents in ring A. In fact, treatment of dimethyl medicagenate (Id) with acetone in the presence of sulfuric acid[11] afforded an acetonide (II) which implied that the second hydroxyl group of the sapogenin had to be located at positions

(1) Paper XXX, A. Sandoval, A. Manjarrez, P. R. Leeming, G. H. Thomas and C. Djerassi, THIS JOURNAL, **79**, 4468 (1957).

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(3) Wayne State University, Detroit, Michigan.

(4) Western Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture, Albany 10, Calif.

(5) E. D. Walter, G. R. Van Atta, C. R. Thompson and W. D. Maclay, THIS JOURNAL, **76**, 2271 (1954).

(6) For pertinent literature see ref. 5.

(7) At the time that this work was undertaken, the structure of only one such dicarboxylic acid—quinovic acid (H. Wieland and M. Erlenbach, *Ann.*, **453**, 83 (1927))—was known. Since that time, the structures of two additional triterpene dicarboxylic acids have been announced, namely, melaleucic acid (H. R. Arthur, A. R. H. Cole, K. J. L. Thieberg and D. E. White, *Chemistry & Industry*, 926 (1956)) and barringtogenic acid (R. Anantaraman and K. S. Madhavan Pillai, *J. Chem. Soc.*, 4369 (1956)).

(8) Several transformation products of medicagenic acid either did not crystallize or did so only with difficulty.

(9) The infrared spectrum of the dimethyl ester Id shows remarkable separation of the ester bands in Nujol mull (see Experimental) which seems to be due to hydrogen bonding, since this is not observed in the corresponding diacetate Ic.

(10) C. Djerassi, E. Farkas, A. J. Lemin, J. C. Collins and F. Walls, THIS JOURNAL, **76**, 2969 (1954).

(11) *Cf.* J. L. Beton, T. G. Halsall and E. R. H. Jones, *J. Chem. Soc.*, 2904 (1956).