methylmerimine, 1.87 ml. of methyl iodide and 15 ml. of ethanol was allowed to stand at room temperature for 5 days and was then heated at reflux for 90 min. The solution was concentrated and then diluted with ether. The precipitate which separated was filtered off and recrystallized from ethanol. The yield of 2-<title>acyclic</title>-7-methoxy-6-methylmerimine methiodide, m.p. 175-177°, was 89%. Anal. Calcd. for C₁₆H₁₇IN₂O₃: C, 41.4; H, 4.92; I, 36.5; N, 8.05. Found: C, 41.4; H, 4.71; I, 36.5; N, 8.27.

The following were prepared by the same general procedure:


2-Acetamido-2-acetyl-6-methylmerimine methiodide: yield 41%, m.p. 198-199°. Anal. Calcd. for C₁₆H₁₈INO₃: C, 41.6; H, 4.84; I, 33.8; N, 11.2. Found: C, 41.7; H, 4.88; I, 33.9; N, 11.0.


2-(<title>Acetoxysulfanil</title>)-7-methoxy-6-methylmerimine (XXIV).—A mixture of 1.18 g. of 7-methoxy-6-methylmerimine dihydrochloride, 1.23 g. of <title>-acetylsulfanil</title> chloride and 30 ml. of 1 N sodium hydroxide was allowed to react at 30-35° for one hour and then heated on the steam-bath for two hours. The precipitate was filtered hot, washed with water, dried and then recrystallized from ethanol. The yield of 2-(<title>Acetoxysulfanil</title>)-7-methoxy-6-methylmerimine, m.p. 212-215°, was 0.7 g. (44%).

The following compounds were prepared by the same general procedure:


7-Methoxy-6-methyl-2-(<title>Acetoxysulfanil</title>)-merimine (XXV).—A mixture of 1.08 g. of the above acetoxyl derivative, 20 ml. of ethanol and 5 ml. of 5 N sodium hydroxide was heated on the steam-bath for one hour. The reaction mixture was concentrated and diluted with water and the precipitate was filtered. On recrystallization from ethanol, 0.55 g. (58%) of 7-methoxy-6-methyl-2-(<title>Acetoxysulfanil</title>)-merimine, m.p. 204-205°, was obtained.

Acknowledgment.—We are indebted to Mr. O. Sundberg and co-workers for the microanalyses.

PEARL RIVER, N. Y.

Alkaloid Studies. XVII.¹ The Structure of the Cactus Alkaloid Pilocereine²

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In contrast to the hitherto known cactus alkaloids which are based on a β-phenylethylamine or tetrahydroisoquinoline skeleton, pilocereine consists of two tetrahydroisoquinoline nuclei fused by an ether linkage. Its exact structure (XIIIa) was elucidated by analogy with alkaloids of known structure. Consequently, it was of particular interest to elucidate the structure of pilocereine, an alkaloid found in various giant cacti and possessing the unusually high (at least for a cactus alkaloid) yield of 37%. The structure elucidation is illustrated by the following examples which also illustrate their resemblance to alkaloids of known structure.

The most remarkable chemical feature of the hitherto studied cactus alkaloids is the simplicity of the various structures which are all based on β-phenylethylamine or 1,2,3,4-tetrahydroisoquinoline. Mescaline (I) and anhalinine (II) can be considered as two examples which also illustrate their close biogenetic origin and even the most compli-
empirical formula C_{59}H_{54}N_{3}O_{4}. The pharmacology of this alkaloid already has been reported, and we should now like to describe the relevant experiments which lead us to propose structure XIIIa as a complete expression for pilocerine.

Of the four oxygen atoms in pilocereine, two are present as methoxyl groups, one as a kryptophenol and the remaining one was believed to be involved in an ether linkage since no infrared hydroxyl or carbonyl bands were noted in pilocereine methyl ether. Further support could now be provided by the observation that while pilocereine contains one active hydrogen atom (kryptophenol), none is present in its methyl ether. The alkaloid remained unchanged after catalytic hydrogenation in ethanol solution using either platinum oxide or palladium-charcoal. Various oxidations led to no conclusive results except for a permanganate oxidation of its methyl ether IVb which furnished as the only recognizable product isobutyric and isovaleric acids, thus implying that pilocereine must contain at least an isobutyl fragment attached to carbon.

The most promising point of attack seemed to be the still uncharacterized ether linkage involving the fourth oxygen atom. On the supposition that this might be a diaryl ether type, we resorted to the sodium-liquid ammonia procedure which has proved to be so fruitful in the field of the bisbenzyl ether. The composition of the products differed depending upon the reaction temperature (-60° as compared to -30°), but in each case separation into phenolic and non-phenolic (including kryptophenolic) material could be accomplished by taking advantage of the differing solubility in alkali.

Irrespective of the temperature at which the potassium-ammonia cleavage of pilocereine was conducted, the principal, phenolic, basic component proved to be an oil which could not be converted into a crystalline derivative. However, after methylation with diazomethane in ether-methanol solution, the oil could be characterized as a crystalline picate and styphnate. The analytical results were consistent with the formulation C_{59}H_{59}N_{3}O_{5} and since functional group analysis indicated the presence of two methoxyl and one N-methyl group, it was clear that one-half of the cleaved pilocereine molecule had now been isolated.

The structure elucidation of the methylated, phenolic cleavage fragment (IVb) of pilocereine proceeded in a straightforward manner along the following lines. Hofmann degradation of IVb led to a methine (V) which furnished formaldehyde upon ozonolysis. Hydrogenation of the methine (V) and repeated Hofmann degradation of VI gave trimethylamine and a neutral substance (VII); ozonolysis of the latter produced isobutyraldehyde. Potassium permanganate oxidation of the original methyl ether IVb yielded a mixture of volatile stench acids (isobutyric and isovaleric acids) and a crystalline acid which was identified as m-hemipinic acid (VIII). This sequence of reactions is only compatible with structure IVb, and this was confirmed by direct comparison with a synthetic specimen of 1-isobutyl-2-methyl-6,7-dimethoxytetrahydroisoquinoline (IVb). In order to define the exact position (C-6 or C-7) of the free phenolic group in the original cleavage product, the substance was ethylated with diazoethane and compared with an authentic (16) sample. It was found (see Experimental portion of this paper) that methylation could be achieved in ether-methanol in 3-5 days and all of the methylations were conducted in this manner even though the phenolic cleavage product IVa could also be methylated in ether without added methanol.

(16) Only one of the two methoxyl groups originated from the alkaloid while the second one was introduced by methylation of the newly formed phenolic function.
pared with the two possible isomers which had recently been synthesized. \(^{(18)}\) The product was shown to be identical with \(\text{l-isobutyl-2-methyl-6-methoxy-7-ethoxy-1,2,3,4-tetrahydroisoquinoline (Ivc)}\) thus proving unequivocally that the free phenolic group was located at C-7 (IVa).

The composition of the alkali-insoluble portion from the pilocereine cleavage was affected by the temperature at which the reaction was conducted. At ca. \(-60\)°, two substances were isolated: the minor constituent, characterized as a crystalline picrate, corresponded to the empirical formula \(\text{C}_{16}\text{H}_{23}\text{NO}\) (one methoxyl group). If this fragment had arisen from the same portion of the pilocereine molecule as the phenolic fragment IVa, it would have to be \(1\text{-isobutyl-2-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (IVd)}\). This assumption was confirmed by direct comparison with a synthetic specimen. \(^{(18)}\)

The second and major base-insoluble component formed a picrate, the analysis of which indicated the empirical formula \(\text{C}_{16}\text{H}_{23}\text{NO}\) for the base. Since the substance possessed only one methoxyl group, it was presumably kryptophenolic (infrared hydroxyl band), and this was established by prolonged methylation with diazomethane \(^{(19)}\) to a new ether lacking free hydroxyl absorption in the infrared. When this methylated, kryptophenolic fragment was subjected to the same reactions (Hofmann degradations and permanganate oxidations) as described above (IVb \(\rightarrow\) VIII) for its phenolic counterpart IVa, the same results were observed (isolation of, respectively, formaldehyde, isobutylaldehyde, isobutyric acid and isovaleric acid) except that no substituted phthalic acid could be obtained. At this stage of the investigation it was simply assumed that the inability to isolate in this case a substituted phthalic acid may have been due to destruction of the aromatic ring activated by methoxyl substituents. Since the phenolic (IVa) and kryptophenolic cleavage products each corresponded to \(\text{C}_{16}\text{H}_{23}\text{NO}\), it appeared that both fragments of the pilocereine molecule (\(\text{C}_{16}\text{H}_{23}\text{NO}\)) had been secured and that only two structures—IX and X—needed to be considered for the alkaloid.

Both hypothetical structures IX and X for pilocereine appeared to be consistent with the cleavage results and with the general properties of the alkaloid. Thus ether cleavage would yield the two fragments IVa and IVd, \(^{(19)}\) already identified by degradation and synthesis, while the kryptophenolic portion would then be represented by either XIa or XIIa. The kryptophenolic character of such a cleavage product and of pilocereine itself could be ascribed to steric hindrance imposed by the bulky isobutyl substituent \(\text{peri}\) to it. However, synthesis \(^{(18)}\) of the methyl ethers Xib and XIIb proved conclusively that pilocereine could not possibly be represented by either IX or X since the synthetic products were different from the methylated, kryptophenolic cleavage base.

An explanation for this apparent inconsistency appeared when the potassium-ammonia cleavage of pilocereine was carried out near \(-30\)°. Under those conditions, in addition to the phenolic (IVa) and “kryptophenolic” fragments, \(^{(20)}\) there was formed an appreciable amount of a colorless, crystalline (m.p. 178°) substance (named “desmethyl-isopilocereine”). The high melting point and in particular the analytical figures (\(\text{C}_{16}\text{H}_{21}\text{NO}\)) demonstrated that this substance was not a cleavage product of pilocereine but rather closely related to it. In fact, it differed from the parent alkaloid only by the absence of one methoxyl group and it was first assumed that it simply represented partially demethylated pilocereine. However, methylation of this substance with diazomethane in ether—methanol yielded an oily substance, the infrared spectrum of which was identical with that of the methylated, kryptophenolic cleavage product “isopilocereine” methyl ether. When a partial methylation was attempted with diazomethane in ether alone, some of the above kryptophenol was isolated as the crystalline picrate. It then became apparent that the kryptophenol (\(\text{isopilocereine}^{(21)}\)) isolated in the original \(-60\)° (as well as in part in the \(-30\)°) cleavage could not possibly possess structures of type XI and XII since it was still dimeric. \(^{(21)}\)

We conclude that the potassium-ammonia cleavage of pilocereine proceeds in part by the expected path to yield \(\text{C}_{16}\) fragments (IVa and IVd) and in part by rearrangement or possibly dimerization of

\(^{(18)}\) Cleavage of an unsymmetrical aryl ether can yield all four possible products (cf. ref. 13). The fourth (tri氧genated) product would contain two free phenolic groups in one ring and might be expected to be unstable. It was never isolated in the cleavage of pilocereine, but it was encountered when the reaction was performed with the methyl ether where no labile polyphenols would be formed.\(^{(20)}\)

\(^{(19)}\) L-isobutyl-2-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (IVd) was not encountered in those experiments.\(^{(21)}\)

\(^{(21)}\) Unfortunately, while the kryptophenol itself gave a crystalline picrate on which a complete analysis (including functional groups) was performed, its methylation product was oily and only C, H and N analyses were secured. When the dimeric nature was recognized, a methoxyl determination was carried out which clearly showed the presence of three methoxyl functions. The methoxyl analysis of the kryptophenol itself was of no help in this connection since it contained two methoxyl groups based on a Ca formula or one methoxyl based on Cb, in agreement with the hypothetical structures XI or XII.
initially formed C₁₅ components to yield an isomer of pilocereine in which the phenolic group is still kryptophenolic (repeated cleavage of this dimer with potassium in liquid ammonia failed). It should be noticed that at the higher temperature (−30°C), rearrangement (or dimerization) is also accompanied by demethylation. The structure of the rearrangement product has not been established, but it is possible that it should be represented by IX as a consequence of the transformation

\[ \text{XIIIa} \rightarrow \text{IX} \]

The high-melting, crystalline product would then be a demethylation product of IX, and it appears quite likely that the two phenolic groups are in different rings since the substance appears to be reasonably stable to oxidation.

The above discussion shows that the only cleavage products of structural value are IVa and IVd. In fact, the absence of any other C₁₅ fragments raises the question whether the principal product—1-isobutyl-2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline (IVa)—might not represent both halves of pilocereine. Such a hypothesis would be accommodated by structure

\[ \text{XIIIA for pilocereine, which would also be eminently satisfactory from a biogenetic viewpoint since exactly the same type of oxygenation is encountered in a variety of bisbenzylisoquinoline alkaloids such as daphnandrine (XIV).} \]

A direct connection between pilocereine (XIIIa) and the bisbenzylisoquinoline alkaloids appeared feasible since the latter (e.g., oxyacanthine) have been degraded to the dialdehyde XVIII. Hofmann degradation of pilocereine methyl ether (XIIIb) proceeded smoothly and the resulting methine XV was hydrogenated to the corresponding crystalline tetrahydro derivative XVI. All attempts to isolate a normal second stage Hofmann product XVII or to oxidize the crude total product to the aldehyde XVIII failed in spite of elimination of trimethylamine. It appears that the predom-
in the unsuccessful Hofmann degradation sequence, attention was directed to the potassium-ammonia cleavage of pilocereine methyl ether (XIIIb). It was felt that if the rearrangement mechanism (XIIIa → IX) or a similar one did indeed obtain in the case of pilocereine (XIIIa), this would be inhibited in pilocereine methyl ether (XIIIb) and furthermore, it might be possible to isolate all of the possible cleavage products. Indeed, the "non-phenolic" portion of such a cleavage of XIIIb could be resolved by chromatography into 1-isobutyl-2-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (IVd), 1-isobutyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IVb) and an oily substance which after methylation affored the known 1-isobutyl-2-methyl-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline (XXb). The phenolic components of the pilocereine methyl ether cleavage were separated after methylation into 6,7-dimethoxy- (IVb) and 6,7,8-trimethoxy- (XXb) 1-isobutyl-2-methyl-1,2,3,4-tetrahydroisoquinoline.

The fact that the trioxigenated cleavage product was isolated in both the phenolic and non-phenolic portions was indicated that the phenolic group in that compound is rather hindered. This would be consistent with structure XXa-hindrance being due to the peri-isobutyl substituent as well as to the adjacent methoxyl group-but could conceivably also apply to a phenol such as XXI in which the free phenol is flanked by methoxyl groups on either side. While either XXa or XXI would afford the same methylation product XXb (the identity of which was established rigorously by synthesis) it should be noted that the presence (prior to methylation) of the 6,7-dimethoxy derivative IVb in the non-phenolic portion requires structure XXa.

The isolation of all four possible cleavage products (IVa, IVb, IVd, XXa) from the potassium-ammonia treatment of pilocereine methyl ether (XIIIb) establishes the structure of that compound. The kryptophenolic nature of pilocereine is compatible only with structure XIIIa, and this was proved rigorously by diary ether cleavage of pilocereine ethyl ether (XIIIc) which yielded the expected products (IVa, IVc, IVd and XXe). It should be noted that considerably more drastic conditions were required in the cleavage of the ethyl ether XIIIc as compared to the lower homolog XIIIb.

While according to structure XIIIa, pilocereine contains two asymmetric centers, it was nevertheless isolated in an optically inactive form. Späth and Keßler already have called attention to the fact that several cactus alkaloids are isolated in the d,l-form and they noted that synthetic, resolved pellotine (III) racemized quite readily, particularly in acid solution. It is impossible to state, therefore, whether pilocereine was racemized during the isolation process or whether it exists in the racemic form in the plant.

The presence of an isobutyl fragment at C-1, as observed in pilocereine (XIIIa), is unique among isoquinoline alkaloids. It strongly points toward the participation of leucine (or its biogenetic equivalent) in the synthesis of this alkaloid in the plant, and it is not impossible that simple 1-isobutyltetrahydroisoquinolines (such as IVa) might be found in those cacti in which pilocereine has been encountered. This would seem particularly likely in the event that diphenyl ether formation should follow tetrahydroisoquinoline ring closure, and we are presently concerned with a search among cacti for such precursors. While isobutyl groups are fairly common among alkaloids, they are usually present as esters and the direct connection of an isobutyl fragment to a non-oxygenated carbon atom does not appear to have been encountered before among alkaloids.

Experimental

Pilocereine (XIIIa) and Pilocereine Methyl Ether (XIIIb).—In order to establish the optical inactivity of pilocereine, its rotation was examined in methanol solution in a Rudolph spectropolarimeter over the range 600-350 ma and no perceptible rotation was noted. New functional group analysis (see ref. 7) indicated the presence of two C-methyl and two N-methyl groups in the alkaloid. Anal. Calcd. for CH$_2$N$_2$O: C=76.03. Found: C=76.05. CH$_2$N$_2$O: N=5.16; active hydrogen, 0.95. An alternative method for the methylation of pilocereine proceeded as follows: pilocereine (8.5 g.) in methanol (200 cc.) and ether (250 cc.) solution was left for 4 days at 0° with 2.2 g. of distilled diazomethane. After adding an additional 2.2 g. of diazomethane and letting stand at 0° for 3 more days, the solvent was removed and the residue was recrystallized from hexane; yield 6.5 g. (in two crops), m.p. 92°-105°, then resolidification and sharp melting at 153-155°. The infrared spectrum (no hydroxyl band) of this methyl ether (XIIIb) was identical with that of the earlier described analytical sample.

(32) In order to make sure that the substance does not just happen to have zero rotation at the sodium D line, it was examined in a spectropolarimeter down to 550 ma without observing any perceptible rotation.

(33) R. Späth and F. Keßler, Ber., 69, 755 (1936).

(34) This is not limited to alkaloids with a free 8-hydroxyl group since this also applies to carbgenine (1,2-dimethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline).

(35) See in particular p. 85 of ref. 5.

(36) For a recent example see W. Deckers and J. Maier, Ber., 68, 1423 (1935).

(37) Melting points were determined on the Kofler block. We are indebted to Mrs. Dolores Phillips for all infrared spectra. Microanalyses were carried out by Dr. Alfred Bernhardt (Mülheim, Germany), Geller Laboratories (Hackensack, N. J.) and Spang Microanalytical Laboratory (Plymouth, Mich.).

(38) In order to secure adequate amounts of pilocereine for the degradation experiments described in this paper, over 100 kg. of the cactus was collected by Dr. R. B. Humphrey (University of Arizona), and the preliminary processing was carried out in the pilot plant of Chas. Pfizer and Co. (Brooklyn, N. Y.). We are grateful for this very valuable assistance.

(39) Application of the Rodionow procedure to pilocereine has already been reported in ref. 7.

Pilocereine methyl ether with m.p. 158-159° could be transformed by recrystallization from ethyl acetate into a second crystalline form with m.p. 138-139°. The transformation was reversed by recrystallization from hexane.

Permanganate Oxidation of Pilocereine Methyl Ether (XIII).—Pilocereine (3.0 g.) in 100 cc. of absolute ethanol was treated with 3.6 g. of distilled diazoethane in ether. The mixture was left in the refrigerator for 6 days. Evaporation of the solvent and recrystallization from hexane gave 2.6 g. of the ethyl ether with m.p. 149-151°. A trace of colored phenolic, non-basic material was discarded, and the mixture was left in the refrigerator for 151°. An additional 0.32 g. (n1,p. 143-148°) was secured by recrystallization from acetone.

For subsequent degradation experiments with "isopilocereine," it was necessary to protect the kryptophenolic group, and 3.5 g. of "isopilocereine" picate was converted into the free base by means of lithium hydroxide and then methylated with diazomethane in ether—methanol by the procedure described above for pilocereine. The resulting isopilocereine" methyl ether (55% yield) was evaporatively distilled at 180-180° and 0.005 mm. and analyzed directly since no crystalline salts could be obtained.

Permanganate Oxidation of Isopilocereine Methyl Ether (XIIIb).—A solution of 2.5 g. of pilocereine methyl ether in 10 cc. of water and 250 g. of sodium bicarbonate followed by 2 l. of water and 250 g. of sodium hydroxide solution to give 0.2 g. of an oil which was chromatographed on 9 g. of neutral alumina and eluted in 9 fractions. Fractions 1 and 2, eluted with benzene, weighed 0.155 g., n\textsubscript{D} 1.5824, and exhibited an infrared spectrum which was indistinguishable from that of synthetic 1-isobutyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IVd) picrate.

Reductive Cleavage of Isopilocereine (XIIIa) with Potassium in Liquid Ammonia at -60°.—A solution of 5.0 g. of isopilocereine in 100 cc. of distilled (from sodium) ammonia with 6 g. of potassium was carried out exactly as described above except that the reaction was conducted at -60°. After separation into its components, there was obtained 1.79 g. of "non-phenolic" basic and 2.68 g. of phenolic, basic fractions. When a dried, ether solution of the latter was concentrated to a small volume, a white, crystalline substance (1.45 g.) crystallized. Further recrystallizations from ethanol the product ("demethylisopilocereine") melted at 177.5-178°, depressed to 160° upon admixture with pilocereine, and showed significant differences in the infrared spectrum, especially the hydroxyl region. The other products were the same as those found in the -60° cleavage.
Desmethyl-isopilocereine probably contains the two phenolic groups in two different rings since the substance was rendered unchanged after attempted oxidation with silver oxide. Partial methylation of desmethyl-isopilocereine was accomplished by treating 100 mg. with 0.5 mg. of sodium methoxide (no methanol present) for 2 days at 0°. Evaporative distillation of the product yielded 81 mg. of a glass, the infrared spectrum of which closely resembled that of isopilocereine. Treatment with picric acid furnished a small amount of isopilocereine picrate, identified by infrared comparison and mixture melting point determination.

Complete methylation of 210 mg. of desmethyl-isopilocereine could be carried out in methanol-ether solution for 7 days, and distillation gave 120 mg. of isopilocereine methyl ether, the infrared spectrum of which was superimposable upon that of the diazomethane methylation product of isopilocereine.

Ethylation of Phenolic, Basic Cleavage Product (1-Isobutyl-2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisquinoline (IVa)) Derived from Pilocereine (XIIIa) — A 300-mg. portion of the phenolic, basic cleavage product (consisting chiefly of IVa) was ethylated with 0.64 g. of diazomethane in methanol for 7 days at room temperature. The product was freed of unreacted phenolic contaminants by washing with alkali, and it was then transformed into its picrate, m.p. 161.5-163.5°, undepressed upon admixture with a synthetic specimen. The mixture was treated with picric acid and furnishing a small amount of isopilocereine picrate, identified by infrared comparison and mixture melting point determination.

Permanente oxidation of isopilocereine methyl ether was carried out in the manner described for pilocereine (XIIIb) to give what is believed to be 1-isobutyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisquinoline (IVb). The methiodide (150 mg.) was dissolved in 5 cc. of methanol and 1 cc. of methyl iodide yielding 153 mg. of dimethiodide, m.p. 191-194° after recrystallization from hexane-acetone.

The above methine (100 mg.) was ozonized in chloroform solution at -60° yielding 55 mg. (61%) of the formaldehyde dimedone derivative. Another portion of the substance (500 mg.) was hydrogenated (10 minutes) in ethanol solution with palladium charcoal catalyst, and the reduced methine was distilled at a bath temperature of 160° and 0.005 mm., yield 450 mg.

Degradation of Methylated, Phenolic, Basic Cleavage Product (1-Isobutyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisquinoline (IVb)) Derived from Pilocereine (XIIIa) — The permanganate oxidation of natural 1-isobutyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisquinoline (IVb) was carried out before the substance had ever been synthesized, since it formed part of the structure proof of this degradation product. However, the experimental details of this oxidation already have been reported for the synthetic substance and hence will not be repeated here for the pilocereine cleavage product. By the reported procedure 2.2 g. of IVb yielded 310 mg. of m-hemipinic acid (Anal. Caled. for C9H10NO4: C, 73.56; H, 9.35; N, 11.89. Found: C, 73.44; H, 9.43; N, 11.79).

The Hofmann degradation was performed on 104 mg. of isopilocereine methyl ether with 5 cc. of methylene chloride and 0.05 ml. of concentrated hydrochloric acid. The product was filtered, the solvent was removed and recrystallized several times from acetonitrile to yield 0.92 g. of oily methine V.

A 185-mg. portion of the methine was ozonized in glacial acetic acid at 15° for 30 minutes, and the reaction mixture was steam distilled into acidified aqueous 2,4-dinitrophenylhydrazine solution. Extraction with benzene and chromatography on neutral alumina yielded by elution with benzene 20 mg. of isobutryraldehyde 2,4-dinitrophenylhydrazone, m.p. 181-185° (recrystallized from methanol), which was not depressed when mixed with an authentic specimen.

Degradation of isopilocereine methyl ether — The permanganate oxidation of isopilocereine methyl ether was carried out in the manner described for pilocereine (XIIIb) to give what is believed to be 1-isobutyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisquinoline (IVb), but except for the volatile stench acids, isobutyric and isovaleric acids, no other acidic fragment could be characterized.

For the Hofmann degradation, 104 mg. of isopilocereine methyl ether was treated in benzene solution for 4.5 hr. with 1 cc. of methyl iodide yielding 158 mg. of dimethiodide, m.p. 191-194° after recrystallization from hexane-acetone.

The above methine (100 mg.) was ozonized in chloroform solution at -60° yielding 55 mg. (61%) of the formaldehyde dimedone derivative. Another portion of the substance (500 mg.) was hydrogenated (10 minutes) in ethanol solution with palladium charcoal catalyst, and the reduced methine was distilled at a bath temperature of 160° and 0.005 mm., yield 450 mg.

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Elimination of trimethylamine proceeded smoothly as demonstrated by the isolation of 0.46 g (75%) of trimethylamine picrate (m.p. 206-210°) but the nitrogen-free degradation product (0.84 g.) apparently contained very little of the desired olefin XVI since treatment with one equivalent of ozone in ethyl acetate solution at -80° by the inverse technique(48) which worked satisfactorily in a model experiment with isoeugenol methyl ether followed by decomposition of the ozone with zinc in acetic acid (24 hr., room temperature) yielded only 3% of isobutyraldehyde, 2,4-dinitrophenylhydrazine after chromatography on bentonite-kieselguhr(49).

Careful examination of the non-volatile portion including chromatography did not yield any of the desired aldehyde XVIII(48) even though seed crystals of authentic dialdehyde (derived from an intermediate(48) kindly provided by Sir A. R. Todd, Cambridge University) were available.

In another experiment, in which the Hofmann degradation of the dimethiodide of 1.72 g. of crystalline reduced methine XVI was carried out as described above with the modification that the dimethiodide was first dissolved in ethanol (rather than being added in the solid state to the alkaline medium), a substance was isolated which on the basis of the analysis of a distilled (155-170°C at 0.05 mm.) sample (no infrared hydroxyl absorption) appeared to be the diethyl ether XIX arising by solvolysis.

**Reductive Cleavage of Pilocereine Methyl Ether (XIIIb)**

**With Potassium in Liquid Ammonia.—**The cleavage of 1.98 g. of pilocereine methyl ether (XIIIb) was carried out in the manner described above with 80 cc. of ether, 600 cc. of liquid ammonia and 2.5 g. of potassium at -60° for 7 hr. and furnished 1.30 g. of "non-phenolic," basic and 0.67 g. of phenolic, basic fractions. The "non-phenolic," basic portion was dissolved in 20 cc. of hexane and chromatographed on 80 g. of alumina (desiccated with 2.4 cc. of 10% acetic acid), collecting a total of 114 fractions.

Fractions 20-46, eluted with hexane up to 1:1 hexane-benzene mixtures, upon treatment with picric acid in ethanolic solution gave 0.33 g. (29%) of the picrate of 1-isobutyl-2-methyl-6,7-dimethoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline (IVd), m.p. 152-153°, 0.227 g. (11.5%) of 1-isobutyl-2-methyl-6,7-dimethoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline (IVb), m.p. 152-153°, and 0.244 g. (12%) of 1-isobutyl-2-methyl-6,7-dimethoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline (IVc) picrate, m.p. 152-153°, and 0.244 g. (12%) of 1-isobutyl-2-methyl-6,7-dimethoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline (IVd) picrate, m.p. 152-153°.

Reductive Cleavage of Pilocereine Ethyl Ether (XIIIc)

**With Potassium in Liquid Ammonia.—**The ethyl ether XIIIc (2.04 g.) was cleaved in 80 cc. of ether and 600 cc. of ammonia with 3.3 g. of potassium at -60°. The reaction time had to be extended to 24 hr. (in contrast to pilocereine or its methyl ether) since incomplete cleavage was observed when the time was shortened. The usual processing gave 1.30 g. of "non-phenolic," basic and 0.51 g. of phenolic, basic fractions.

Careful chromatography of the "non-phenolic" portion as described above for the methyl ether cleavage gave in order of increased polarity 0.570 g. (32%) of 1-isobutyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IVb) picrate, m.p. 151-153°, 0.227 g. (11.5%) of 1-isobutyl-2-methyl-6,7-dimethoxy-7-ethoxy-1,2,3,4-tetrahydroisoquinoline (IVd) picrate, m.p. 152-153°, and 0.244 g. (12%) of 1-isobutyl-2-methyl-6,7-dimethoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline (XXc) picrate, m.p. 153-154°.

Identity of the first two compounds was established by mixture melting point determination of the picrates as well as by infrared comparison of the free bases with those of synthetic samples. The structure of the third compound follows from its analysis, the presence of a free hydroxyl in the infrared spectrum of the free base and from the constitution of pilocereine itself.

**Reductive Cleavage of Pilocereine Ethyl Ether (XIIIc)**

**With Potassium in Liquid Ammonia.—**The ethyl ether XIIIc (2.04 g.) was cleaved in 80 cc. of ether and 600 cc. of ammonia with 3.3 g. of potassium at -60°. The reaction time had to be extended to 24 hr. (in contrast to pilocereine or its methyl ether) since incomplete cleavage was observed when the time was shortened. The usual processing gave 1.30 g. of "non-phenolic," basic and 0.51 g. of phenolic, basic fractions.

Careful chromatography of the "non-phenolic" portion as described above for the methyl ether cleavage gave in order of increased polarity 0.570 g. (32%) of 1-isobutyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IVb) picrate, m.p. 151-153°, 0.227 g. (11.5%) of 1-isobutyl-2-methyl-6,7-dimethoxy-7-ethoxy-1,2,3,4-tetrahydroisoquinoline (IVd) picrate, m.p. 152-153°, and 0.244 g. (12%) of 1-isobutyl-2-methyl-6,7-dimethoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline (XXc) picrate, m.p. 153-154°. Identity of the first two compounds was established by mixture melting point determination of the picrates as well as by infrared comparison of the free bases with those of synthetic samples. The structure of the third compound follows from its analysis, the presence of a free hydroxyl in the infrared spectrum of the free base and from the constitution of pilocereine itself.

**Analytical Calculations**

For C₂₂H₂₈N₂O₆: C, 52.87; H, 5.79; N, 10.72; O, 30.62.

Methylation of the phenolic, basic cleavage fraction (0.51 g.) in the standard manner and treatment with picric acid gave 0.566 g. (19%) of the pure picrate (m.p. 183-185°) of 1-isobutyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, identical in all respects with a synthetic sample.

Detroit, Michigan