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-acetyl-7-methoxy-6-methylmerimine methiodide, m.p. 175–177°, was 89%.

Anal. Calcd. for $C_{12}H_{17}IN_2O_2$: 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:

7-Acetoxy-2-acetyl-6-methylmerimine methiodide: yield 61%, m.p. 222–224°. *Anal.* Calcd. for $C_{13}H_{17}IN_2O_3$: C, 41.5; H, 4.56; I, 33.8; N, 7.45. Found: C, 41.4; H, 4.53; I, 33.6; N, 7.55.

7-Acetamido-2-acetyl-6-methylmerimine methiodide: yield 41%, m.p. 198–199°. *Anal.* Calcd. for $C_{13}H_{18}IN_3O_2$: C, 41.6; H, 4.84; I, 33.8; N, 11.2. Found: C, 41.7; H, 4.88; I, 32.9; N, 11.0.

2-Carbethoxy-6-methylmerimine methiodide: yield 54%, m.p. 183–185°. *Anal.* Calcd. for $C_{12}H_{17}IN_2O_2$: C, 41.4; H, 4.92; I, 36.5; N, 8.05. Found: C, 41.1; H, 4.62; I, 36.4; N, 7.78.

2-(*p*-Acetylsulfanilyl)-7-methoxy-6-methylmerimine (XXIV).—A mixture of 1.18 g. of 7-methoxy-6-methylmerimine dihydrochloride, 1.23 g. of *p*-acetylsulfanilyl 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-(*p*-acetylsulfanilyl)-7-methoxy-6-methylmerimine, m.p. 212–213°, was 0.7 g. (44%).

Anal. Calcd. for $C_{17}H_{19}N_3O_4S$: C, 56.5; H, 5.30; N, 11.6; S, 8.85. Found: C, 56.7; H, 5.14; N, 11.4; S, 8.85.

The following compounds were prepared by the same general procedure:

2-(*p*-Acetylsulfanilyl)-7-hydroxy-6-methylmerimine: yield 35%, m.p. above 250°. *Anal.* Calcd. for $C_{16}H_{17}N_3O_4S$: C, 55.3; H, 4.93; N, 12.1; S, 9.23. Found: C, 55.2; H, 4.93; N, 11.9; S, 9.03.

2-(*p*-Acetylsulfanilyl)-7-amino-6-methylmerimine hemihydrate: yield 75%, m.p. above 280°. *Anal.* Calcd. for $C_{16}H_{18}N_4O_3S\cdot 0.5H_2O$: C, 54.1; H, 5.38; N, 15.8; S, 9.02. Found: C, 54.4; H, 5.05; N, 15.7; S, 8.85.

7-Methoxy-6-methyl-2-(*p*-sulfanilyl)-merimine (XXV).—A mixture of 1.08 g. of the above acetyl 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-(*p*-sulfanilyl)-merimine, m.p. 204–205°, was obtained.

Anal. Calcd. for $C_{15}H_{17}N_3O_3S$: C, 56.4; H, 5.37; N, 13.2; S, 10.0. Found: C, 56.4; H, 5.11; N, 13.5; S, 9.60.

7-Amino-6-methyl-2-(*p*-sulfanilyl)-merimine.—This compound was prepared as above from 2-(*p*-acetylsulfanilyl)-7-amino-6-methylmerimine. The yield was 80%, m.p. 217° dec.

Anal. Calcd. for $C_{14}H_{16}N_4O_2S$: C, 55.2; H, 5.30; N, 18.4; S, 10.5. Found: C, 55.0; H, 5.32; N, 18.6; S, 10.9.

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

PEARL RIVER, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

Alkaloid Studies. XVII.[1] The Structure of the Cactus Alkaloid Pilocereine[2]

BY CARL DJERASSI, S. K. FIGDOR,[3a] J. M. BOBBITT[3b] AND F. X. MARKLEY[3c]

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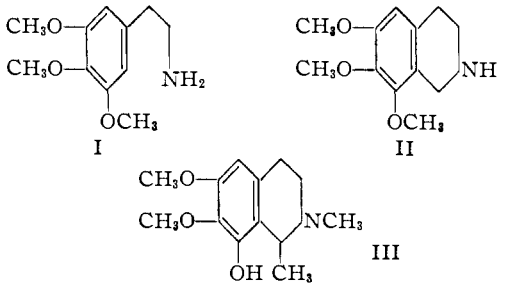
In contrast to the hitherto known cactus alkaloids which are based on a β-phenylethylamine or tetrahydroisoquinoline skeleton, pilocereine consists of two tetrahydroisoquinoline nuclei fused by an ether linkage. Its exact structure (XIIIa) was elucidated by diaryl ether cleavage of pilocereine methyl and ethyl ether with potassium in liquid ammonia and identification of all of the cleavage products. Attention is called to the presence of the 1-isobutyl substituent, which appears to be unique in alkaloid chemistry, and to certain side reactions in the potassium–ammonia cleavage of diaryl ethers.

The most remarkable chemical feature of the hitherto studied cactus alkaloids[4] 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 offered as two examples which also illustrate their close biogenetic origin[5] and even the most complicated cactus alkaloid, pellotine (III) contains only thirteen carbon atoms and one nitrogen atom.



Consequently, it was of particular interest to elucidate the structure of pilocereine, an alkaloid found[6–8] in various giant cacti and possessing the unusually high (at least for a cactus alkaloid)

(1) Paper XVI, C. Djerassi, J. Fishman, M. Gorman, J. P. Kutney and S. C. Pakrashi, THIS JOURNAL, **79**, 1217 (1957).

(2) Our initial studies in this field were supported by a grant-in-aid from the American Heart Association, Inc. Subsequently, financial assistance was provided by the National Heart Institute ot fhe U. S. Public Health Service (Grant No. H-2040).

(3) (a) Postdoctorate Research Fellow, 1953–1954; (b) Postdoctorate Research Fellow, 1955–1956; (c) Predoctorate Research Fellow, 1955–1956.

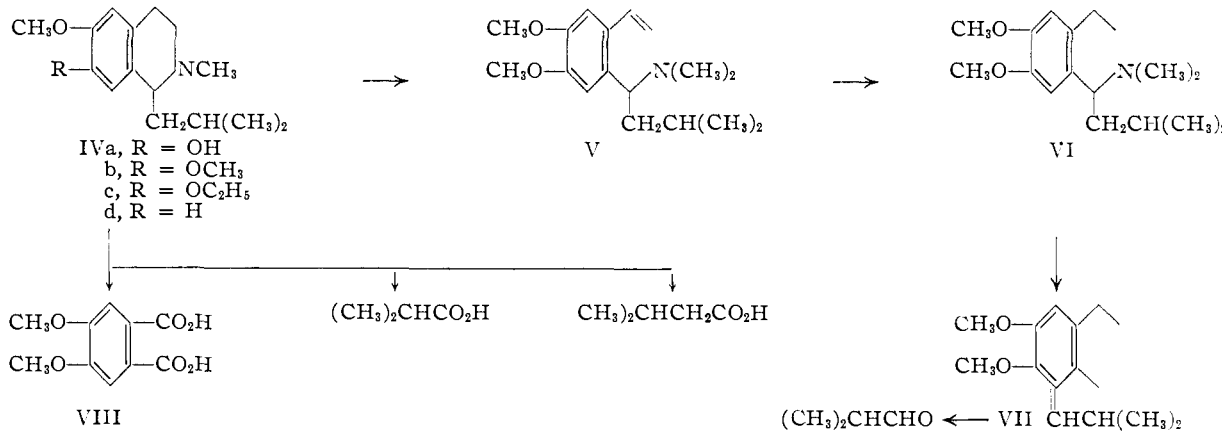
(4) For recent reviews see L. Reti in L. Zechmeister's "Progress in the Chemistry of Organic Natural Products," Vol. VI, Springer, Vienna, 1950, pp. 242–289, and L. Reti in R. H. F. Manske and H. L. Holmes, "The Alkaloids," Vol. IV, Academic Press, Inc., New York, N. Y., 1954, pp. 7–28.

(5) It is now generally accepted that 1,2,3,4-tetrahydroisoquinolines are formed in the plant from substituted β-phenylethylamines and an appropriate amino acid or equivalent (α-keto acid, aldehyde, etc.), the latter providing carbon atom 1 and any substituent attached to it. For pertinent review see R. Robinson, "The Structural Relations of Natural Products," Oxford University Press, 1955.

(6) G. Heyl, *Arch. Pharm.*, **239**, 451 (1901). Heyl did not obtain the alkaloid in crystalline form, but he did arrive at the correct empirical formula (*cf.* ref. 9).

(7) C. Djerassi, N. Frick and L. E. Geller, THIS JOURNAL, **75**, 3632 (1953).

(8) C. Djerassi, C. R. Smith, S. P. Marfey, R. N. McDonald, A. J. Lemin, S. K. Figdor and H. Estrada, *ibid.*, **76**, 3215 (1954).



empirical formula $C_{30}H_{44}N_2O_4$.[9] The pharmacology of this alkaloid already has been reported,[10] and we should now like to describe the relevant experiments[11] which lead us to propose structure XIIIa as a complete expression for pilocereine.

Of the four oxygen atoms in pilocereine, two are present as methoxyl groups, one as a kryptophenol and the remaining one was believed[7] 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 which furnished as the only recognizable products[12] 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[13] which has proved to be so fruitful in the field of the bisbenzyl isoquinoline alkaloids and related bases.[14] The standard conditions[13] proved somewhat unsatisfactory due to incomplete reaction, but replacement of potassium[14] for sodium and extending the reaction time led to complete cleavage of the molecule. 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,[15] the oil could be characterized as a crystalline picrate and styphnate. The analytical results were consistent with the formulation $C_{16}H_{25}NO_2$, and since functional group analysis indicated the presence of two methoxyl[16] 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).[17] 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 com-

(9) The analytical results of the crystalline alkaloid and its salts (ref. 7) were in better agreement with a $C_{30}H_{42}N_2O_4$ formulation, but the present structure proof clearly shows that two additional hydrogen atoms are required. Furthermore, a new N-methyl determination shows that two (rather than one—see ref. 7) such groups are present.

(10) C. E. Powell and K. K. Chen, *J. Am. Pharm. Assoc.*, **45**, 559 (1956).

(11) A preliminary communication concerning part of this work has already been published (C. Djerassi, S. K. Figdor, J. M. Bobbitt and F. X. Markley, THIS JOURNAL, **78**, 3861 (1956)).

(12) This observation was first made in this Laboratory by Dr. Nelly Frick while working on the initial characterization of pilocereine (ref. 7).

(13) P. A. Sartoretto and F. J. Sowa, THIS JOURNAL, **59**, 603 (1937); A. L. Kranzfelder, J. J. Verbanc and F. J. Sowa, *ibid.*, **59**, 1488 (1937); F. C. Weber and F. J. Sowa, *ibid.*, **60**, 94 (1938).

(14) For leading references see M. Tomita in L. Zechmeister's "Progress in the Chemistry of Organic Natural Products," Vol. IX, Springer, Vienna, 1952, pp. 175–224.

(15) It was reported earlier (ref. 7) that pilocereine was not methylated in ethereal solution by diazomethane (24 hr.) and that the Rodionow methylation procedure had to be used. Subsequently, it was found (see Experimental portion of this paper) that methylation could be achieved in ether–*methanol* in 3–7 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.

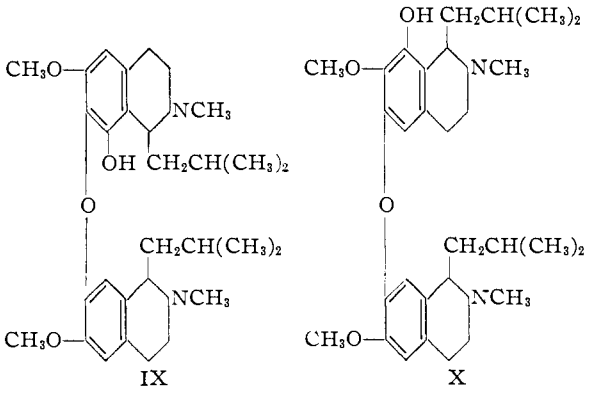
(16) Only one of the two methoxyl groups originated from the alkaloid while the second one was introduced by methylation of the newly formed phenolic function.

(17) C. Djerassi, J. J. Beereboom, S. P. Marfey and S. K. Figdor, THIS JOURNAL, **77**, 484 (1955).

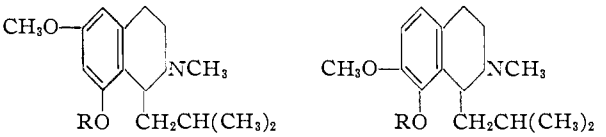
pared with the two possible isomers which had recently been synthesized.[18] The product was shown to be identical with 1-isobutyl-2-methyl-6-methoxy-7-ethoxy-1,2,3,4-tetrahydroisoquinoline (IVc) thus proving unequivocally that the free phenolic group was located at C-7 (IVa).

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 $C_{15}H_{23}NO$ (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-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 $C_{15}H_{23}NO_2$ 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[15] 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 → VIII) for its phenolic counterpart IVa, the same results were observed (isolation of, respectively, formaldehyde, isobutyraldehyde, 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 $C_{15}H_{23}NO_2$, it appeared that both fragments of the pilocereine molecule ($C_{30}H_{44}N_2O_4$) 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 *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.



XIa, R = H
b, R = CH_3

XIIa, R = H
b, R = CH_3

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 "desmethylisopilocereine"). The high melting point and in particular the analytical figures ($C_{29}H_{42}N_2O_4$) 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 ("isopilocereine") 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 C_{15} fragments (IVa and IVd) and in part by rearrangement or possibly dimerization of

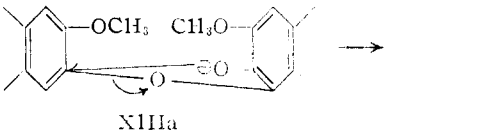
(18) C. Djerassi, F. X. Markley and R. Ehrlich, *J. Org. Chem.*, **21**, 975 (1956).

(19) Cleavage of an unsymmetrical aryl ether can yield all four possible products (*cf.* ref. 13). The fourth (trioxygenated) 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.

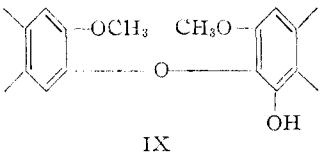
(20) 1-Isobutyl-2-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (IVd) was not encountered in those experiments.

(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 C_{30} formula or one methoxyl based on C_{15}, in agreement with the hypothetical structures XI or XII.

initially formed C_{15} 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°), 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[22] as a consequence of the transformation



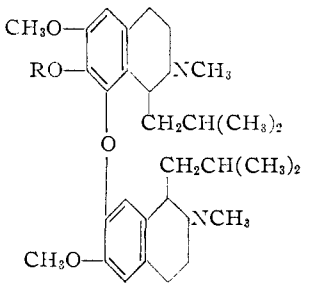
XIIIa



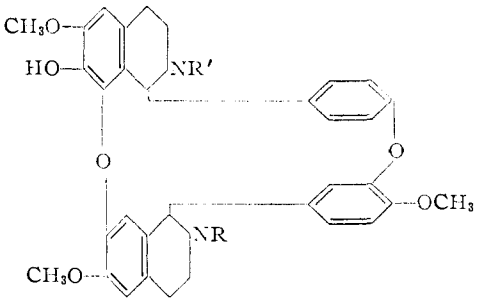
IX

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 C_{15} 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



XIIIa, R = H
b, R = CH_3
c. R = C_2H_5

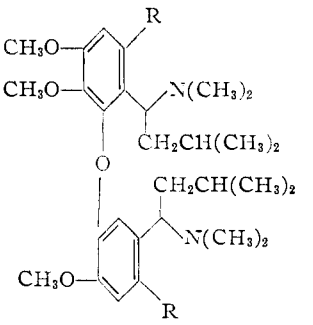


XIV, R = CH_3; R′ = H or
R = H; R′ = CH_3

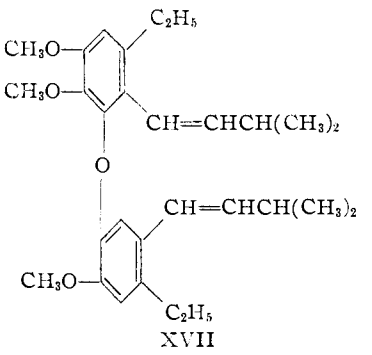
(22) Such a reaction (related to the Smiles rearrangement) has been observed (*cf.* J. D. Loudon, J. R. Robertson, J. N. Watson and S. D. Aiton, *J. Chem. Soc.*, 55 (1950)) in an *o*-hydroxydiphenyl ether with a *p*′-nitro group. In the present case the driving force would have to be ascribed to steric factors since no electron-withdrawing substituents are present.

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[14] such as daphnandrine (XIV).[23]

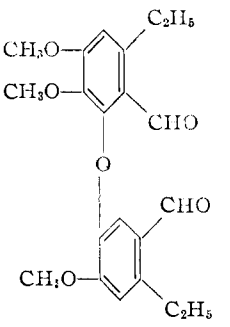
A direct connection between pilocereine (XIIIa) and the bisbenzylisoquinoline alkaloids appeared feasible since the latter (*e.g.*, oxyacanthine) have been degraded[14,24] to the dialdehyde XVIII. Hofmann degradation of pilocereine methyl ether (XIIIb) proceeded smoothly and the resulting methine XV[25] was hydrogenated to the corresponding crystalline tetrahydro derivative XVI. All attempts to isolate a normal second stage Hofmann product XVII[26] or to oxidize the crude total product to the aldehyde XVIII failed in spite of elimination of trimethylamine. It appears that the predom-



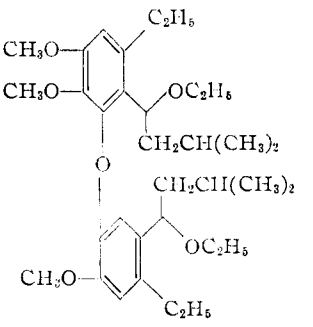
XV, R = CH = CH_2
XVI, R = C_2H_5



XVII



XVIII



XIX

(23) I. R. C. Bick, E. S. Ewen and A. R. Todd, *J. Chem. Soc.*, 2767 (1949).

(24) *Cf.* F. v. Bruchhausen, H. Oberembt and A. Feldhaus, *Ann.*, **507**, 144 (1933).

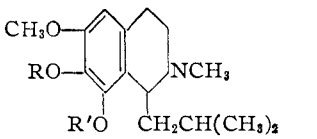
(25) Its structure was confirmed by ozonolysis to formaldehyde without any formation of isobutyraldehyde.

(26) Only traces of isobutyraldehyde were obtained when the crude Hofmann product was ozonized.

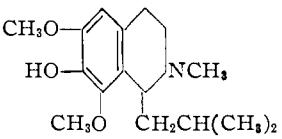
inant course of the reaction was solvolysis[27] aided by the *p*-methoxy substituent, and in one reaction conducted in the presence of ethanol, a product corresponding by analysis to the ethyl ether XIX was isolated.

In view of 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.[19] 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[15] afforded the known[18] 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 trioxygenated cleavage product was isolated in both the phenolic and non-phenolic portions indicates 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[18]) 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.



XXa, R = CH_3; R′ = H
b, R = R′ = CH_3
c, R = C_2H_5; R′ = H



XXI

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 diaryl ether cleavage of pilocereine *ethyl* ether (XIIIc) which yielded the expected products (IVa, IVc, IVd and XXc). 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.

(27) *Cf.* G. Norcross and H. T. Openshaw, *J. Chem. Soc.*, 1174 (1949); A. R. Battersby and H. T. Openshaw, *ibid.*, S59 (1949); A. R Battersby and R. Binks, *ibid.*, 2889 (1955).

While according to structure XIIIa, pilocereine contains two asymmetric centers, it was nevertheless isolated in an optically inactive form.[28] Späth and Kesztler[29] already have called attention to the fact that several cactus alkaloids are isolated in the *d,l*-form[30] 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,[5] and it is not impossible that simple 1-isobutyltetrahydroisoquinolines (such as IVa) might be found in those cacti in which pilocereine has been encountered.[6–8] This would seem particularly likely in the event that diphenyl ether formation[31] 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[32] 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[33]

Pilocereine (XIIIa) and Pilocereine Methyl Ether (XIIIb).[34]—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 mμ 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 $C_{30}H_{44}N_2O_4$: $-CH_3$, 3.03. Found: $C-CH_3$, 4.76, 5.18; $N-CH_3$, 5.16; active hydrogen, 0.95.

An alternative method[35] for the methylation of pilocereine proceeded as follows: pilocereine (8.5 g.) in methanol (200 cc.)–ether (280 cc.) solution was left for six 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[7,35] analytical sample.

(28) 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 350 mμ without observing any perceptible rotation.

(29) E. Späth and F. Kesztler, *Ber.*, **69**, 755 (1936).

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

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

(32) For a recent example see W. Deckers and J. Maier, *Ber.*, **86**, 1423 (1953).

(33) 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.).

(34) 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. R. 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.

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

Anal. Calcd. for $C_{31}H_{46}N_2O_4$: active hydrogen, 0.0. Found: active hydrogen, 0.0.

Pilocereine methyl ether with m.p. 153–155° could be transformed by recrystallization from ethyl acetate into a second crystalline form with m.p. 133–135°. The transformation was reversed by recrystallization from hexane.

Pilocereine Ethyl Ether (XIIIc).—Pilocereine (3.0 g.) in 100 cc. of absolute ethanol was treated with 3.6 g. of distilled diazoethane[36] in 150 cc. of ether. After 24 hr. at room temperature, an additional 3.6 g. of diazoethane in ether was added, and the mixture was left in the refrigerator for 6 days. Evaporation of the solvent and recrystallization from hexane gave 2.07 g. of the ethyl ether with m.p. 149–151°. An additional 0.32 g. (m.p. 143–148°) was secured by chromatography of the mother liquors. The analytical sample, recrystallized from hexane, showed a dual m. p. 90–95° and 152–153°.

Anal. Calcd. for $C_{32}H_{48}N_2O_4$: C, 73.24; H, 9.22; N, 5.34; O, 12.20; 2 N-CH_3, 5.72. Found: C, 72.64; H, 9.23; N, 5.37; O, 12.68; N-CH_3, 5.86.

Regeneration of Bases from Picrates and Styphnates by Ion Exchange Method.[37]—The following procedure was used throughout this work for the regeneration of amines from their picrate or styphnate salts: The bicarbonate salt (IRA-400-HCO_3) of the strongly basic anion exchange resin IRA-400 was prepared by passing 500 cc. of 5% sodium hydroxide solution over 200 g. of IRA-400 hydrochloride followed by 2 l. of water and 250 g. of sodium bicarbonate in saturated aqueous solution. The resin was washed with 12–16 l. of distilled water and stored under distilled water.

The styphnate or picrate salt was dissolved in acetone (or ethanol) containing about 5% of water and passed dropwise over a column of IRA-400-HCO_3. The spent resin turned bright red when acetone was used as the solvent. The column was washed with twice its volume of 10% aqueous acetone, the acetone was removed *in vacuo*, acid was added, the aqueous solution was washed with ether (discarded), made basic with ammonia and the free base was extracted with ether.

Permanganate Oxidation of Pilocereine Methyl Ether (XIIIb).—A solution of 2.5 g. of pilocereine methyl ether in 100 cc. of 10% sulfuric acid was made just alkaline with 2 *N* sodium hydroxide and then treated dropwise at room temperature with 2% aqueous potassium permanganate solution until a purple color persisted (250 cc.). After standing overnight, the colorless solution was acidified with sulfuric acid, extracted continuously with ether and the resulting acids were transformed *via* their acid chlorides (thionyl chloride procedure) into the anilides. Chromatography in the earlier described manner[17] yielded 35 mg. of isobutyric acid anilide and 10 mg. of isovaleric acid anilide. Identification was accomplished by mixture melting point determination and infrared comparison with authentic specimens. It should be noted that it has already been demonstrated[17] that oxidation of isovaleric acid under these conditions does not yield isobutyric acid.

Reductive Cleavage of Pilocereine (XIIIa) with Potassium in Liquid Ammonia at −60°.—A solution of 5.0 g. of pilocereine in 200 cc. of dry ether was added slowly with stirring to 1.5 l. of redistilled liquid ammonia cooled to −60°. Potassium metal (6 g.) was then added rapidly in small pieces and after continued stirring at −60° for 5 hr., the temperature was allowed to rise to −30° over a period of 3 hr. Anhydrous ammonium chloride was added cautiously until the blue color had been discharged. Stirring was stopped, the solvent was allowed to evaporate overnight and the residue was partitioned between ether and 3% sodium hydroxide solution. The alkaline layer was acidified with 40% sulfuric acid, extracted with ether to remove a trace of colored phenolic, non-basic material and then made basic with concentrated ammonium hydroxide. Extraction with ether, washing with water, drying and evaporation yielded 2.46 g. of *phenolic, basic* oil.

The original ether layer was extracted with 10% hydrochloric acid, dried and evaporated to yield a small amount of non-phenolic, non-basic oil which was discarded. The acid extracts were made basic with ammonium hydroxide and extracted with ether to furnish 2.40 g. of a *"non-phenolic," basic* glassy (rather than mobile) fraction.

This non-phenolic, basic fraction consisted chiefly of one substance—"**isopilocereine**" (**IX**)—as demonstrated by chromatography and infrared examination of various fractions. It could be converted without chromatography into a crystalline, yellow *dipicrate* which melted at 235–237° after recrystallization from acetone.

Anal. Calcd. for $C_{42}H_{50}N_8O_{18}$: C, 52.82; H, 5.28; N, 11.73; 2 OCH_3, 6.51; 2 N-CH_3, 3.15. Found: C, 53.20; H, 5.36; N, 11.73; OCH_3, 6.48; N-CH_3, 3.19.

For subsequent degradation experiments with "isopilocereine," it was necessary to protect the kryptophenolic group, and 3.5 g. of "isopilocereine" picrate was converted into the free base by means of lithium hydroxide[38] 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 180–190° and 0.005 mm. and analyzed directly since no crystalline salts could be obtained.

Anal. Calcd. for $C_{31}H_{46}N_2O_4$: C, 72.90; H, 9.08; N, 5.49; 3 OCH_3, 18.28; 2 N-CH_3, 5.88. Found: C, 72.58; H, 9.21; N, 5.40; OCH_3, 17.76; N-CH_3, 5.63.

In one experiment where rearrangement to "isopilocereine" (IX) was very much reduced and cleavage of the molecule appeared to be nearly complete,[39] treatment of a 75-mg. aliquot of the non-phenolic, basic fraction with picric acid (40 mg.) led to a new picrate (70 mg.), which after two recrystallizations from methanol exhibited m.p. 150–151°. It was identified by mixture melting point determination with a sample of synthetic picrate[18] and by infrared comparison of the free bases as **1-isobutyl-2-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline** (**IVd**) picrate.

Anal. Calcd. for $C_{21}H_{26}N_4O_8$: C, 54.54; H, 5.67; N, 12.12. Found: C, 54.96; H, 5.85; N, 12.03.

A 0.26-g. portion of the phenolic, basic cleavage product, which could not be converted into a crystalline salt, was treated with ethereal diazomethane (containing a small amount of methanol) for 6 days at 0°. The solvent was evaporated, the residue extracted with ether and washed with 3% 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., $n^{25}D$ 1.5284, and exhibited an infrared spectrum which was indistinguishable from that of synthetic[17] **1-isobutyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline** (**IVb**). The melting points of the crystalline styphnate (m.p. 212–213°) and picrate (m.p. 184–185°, analysis given below) were not depressed upon admixture with synthetic specimens[17] of these salts.

Anal. Calcd. for $C_{22}H_{28}N_4O_8$: C, 53.65; H, 5.73; N, 11.38; 2 OCH_3, 12.70; N-CH_3, 3.26. Found: C, 54.17; H, 5.67; N, 11.74; OCH_3, 12.51; N-CH_3, 3.20.

Reductive Cleavage of Pilocereine (XIIIa) with Potassium in Liquid Ammonia at −30°.—The cleavage of 5 g. of pilocereine in 1.5 l. of redistilled (from sodium) ammonia with 6 g. of potassium was carried out exactly as described above except that the reaction was conducted at −30°. 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, ethereal solution of the latter was concentrated to a small volume, a white, crystalline substance (1.45 g.) precipitated. After two recrystallizations from ethanol the product ("**desmethylisopilocereine**") melted at 177.5–178°, depressed to 150° 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.

Anal. Calcd. for $C_{29}H_{42}N_2O_4$: C, 72.16; H, 8.77; N, 5.80; O, 13.26; OCH_3, 6.44; 2 N-CH_3, 6.23; mol. wt., 482. Found: C, 72.20; H, 8.86; N, 5.89; O, 13.85; OCH_3, 6.72; N-CH_3, 6.30; neut. equiv. (perchloric acid titration). 244; Rast mol. wt., 383.

(36) Prepared from 13 g. of N-ethyl-N-nitrosourethan according to A. L. Wilds and A. L. Meader, *J. Org. Chem.*, **13**, 763 (1948), and H. von Pechmann, *Ber.*, **31**, 2640 (1898).

(37) The general utility of this procedure is being investigated further by J.M.B. at the University of Connecticut.

(38) A. Burger, THIS JOURNAL, **67**, 1615 (1945).

(39) We can offer no explanation for this difference since the experimental conditions were the same as far as could be determined.

Desmethyl-isopilocereine probably contains the two phenolic groups in two different rings since the substance was recovered unchanged after attempted oxidation with silver oxide.[40]

Partial methylation of desmethyl-isopilocereine was accomplished by treating 100 mg. with excess diazomethane in ether solution (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" (IX); 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-tetrahydroisoquinoline (IVa)) Derived from Pilocereine (XIIIa).—A 300-mg. portion of the phenolic, basic cleavage product (consisting chiefly of IVa) was ethylated with 0.84 g. of diazoethane in ether solution 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. 151.5–152.5°, undepressed upon admixture with a synthetic specimen[18] of **1-isobutyl-2-methyl-6-methoxy-7-ethoxy-1,2,3,4-tetrahydroisoquinoline (IVc) picrate.** Identity was established further by infrared comparison of the respective free bases.

Anal. Calcd. for $C_{23}H_{30}N_4O_9$: C, 54.54; H, 5.97; N, 11.06. Found: C, 54.66; H, 5.94; N, 11.07.

Degradation of Methylated, Phenolic, Basic Cleavage Product (1-Isobutyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IVb)) Derived from Pilocereine (XIIIa).—The permanganate oxidation of natural 1-isobutyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (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[17] for the synthetic substance and hence will not be repeated here for the pilocereine cleavage product. By the reported[17] procedure 2.2 g. of IVb yielded 310 mg. of *m*-hemipinic acid (*Anal.* Calcd. for $C_{10}H_{10}O_6$: C, 53.10; H, 4.46; neut. equiv., 113. Found: C, 53.36; H, 4.65; neut. equiv., 117), which was further characterized as the dimethyl ester, m.p. 89.5–90°. Isobutyric and isovaleric acids, the other products of this oxidation, were identified as their anilides.

The Hofmann degradation was performed on 2.47 g. of methyl ether IVb which was converted into its gummy methiodide by standing overnight at room temperature with 10 cc. of methyl iodide. The methiodide (5.17 g.) was dissolved in a small amount of water, added to 120 cc. of 50% aqueous potassium hydroxide solution and heated under reflux for 2 hr. Isolation in the usual manner yielded 2.05 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 a methanol (distilled from 2,4-dinitrophenylhydrazine) solution of dimedone. After 24 hr. at 0°, 39 mg. (25%) of the formaldehyde derivative crystallized, m.p. and mixture m.p. 193–195°.

The bulk (1.87 g.) of the methine V was hydrogenated in methanol solution with 5% palladized charcoal catalyst, 1 hr. being required for the uptake of one equivalent of hydrogen. The catalyst was filtered, the solvent was removed and the reduced methine VI was evaporatively distilled at 0.1 mm.

Anal. Calcd. for $C_{17}H_{29}NO_2$: C, 73.07; H, 10.46; N, 5.01. Found: C, 72.81; H, 10.02; N, 4.96.

Conversion of the methine VI to the gummy methiodide (3.94 g.) and repeated decomposition by boiling with 50% aqueous potassium hydroxide yielded 1.06 g. of a neutral, nitrogen-free oil, evidently VII. A 90-mg. portion of it was ozonized as described above for V, 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 isobutyraldehyde 2,4-dinitrophenylhydrazone, m.p. 181–183° (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 (XIIIa) and 1-isobutyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (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 153 mg. of dimethiodide, m.p. 191–194° after recrystallization from hexane–acetone.

Anal. Calcd. for $C_{33}H_{52}N_2I_2O_4$: C, 49.82; H, 6.59; N, 3.52. Found: C, 50.01; H, 7.12; N, 3.10.

The methiodide (150 mg.) was dissolved in 5 cc. of methanol and 20 cc. of water and passed four times over a column (12 × 300 mm.) of IRA-400-OH anion exchange resin.[41] The column was washed with 20 cc. of 50% aqueous methanol, and the residue from the combined eluates was distilled at 170–175° and 0.005 mm. yielding 89 mg. of a gummy methine.

Anal. Calcd. for $C_{33}H_{50}N_2O_4$: C, 73.56; H, 9.35; N, 5.20; 2 C-CH_3, 5.59. Found: C, 73.44; H, 9.43; N, 5.12; C-CH_3, 3.97.

The above methine (100 mg.) was ozonized in chloroform solution at −60° yielding 55 mg. (51%) of the formaldehyde dimedone derivative. Another portion of the methine (500 mg.) was hydrogenated (10 minutes) in ethanol solution with palladized charcoal catalyst, and the reduced methine was distilled at a bath temperature of 160° and 0.005 mm., yield 450 mg.

Anal. Calcd. for $C_{33}H_{54}N_2O_4$: C, 73.02; H, 10.03; N, 5.16; O, 11.79; 3 OCH_3, 17.18. Found: C, 72.31; H, 9.87; N, 5.19; O, 12.46; OCH_3, 17.91.

The reduced methine (130 mg.) was transformed into its dimethiodide (180 mg.) with methyl iodide in ether solution, and it was decomposed without further purification[42] by the ion exchange resin method[41] as described above for the first stage Hofmann degradation. The resulting neutral olefin (76 mg.), which was distilled at 160–180° and 0.005 mm., was again ozonized at −60° in chloroform solution, and the distillate was passed into 2,4-dinitrophenylhydrazine solution yielding 44% of isobutyraldehyde 2,4-dinitrophenylhydrazone. Efforts to isolate any substituted diphenyl ether acids from the non-volatile ozonolysis products proved fruitless.

Hofmann Degradation of Pilocereine Methyl Ether (XIIIb).—Pilocereine methyl ether (2.56 g.) was transformed in quantitative yield into its methiodide (3.9 g., m.p. 137–150° dec.) which without further purification was added as a powdered solid to 100 cc. of refluxing 40% sodium hydroxide solution and boiled for 2.5 hr. Structure XV for the resulting methine (2.0 g., 77% yield) was established by ozonolysis of a 160-mg. portion in acetic acid solution and steam distillation into 2,4-dinitrophenylhydrazine solution. Only formaldehyde 2,4-dinitrophenylhydrazone (47 mg., 56% yield) was isolated, uncontaminated by any isobutyraldehyde derivative.

Pilocereine methyl ether methine (XV) (1.9 g.) was hydrogenated in 50 cc. of 95% ethanol with 300 mg. of 10% palladized charcoal catalyst and the product (1.85 g.) was recrystallized several times from acetonitrile to yield 0.92 g. of the reduced methine XVI, m.p. 101.5–103.5°.

Anal. Calcd. for $C_{33}H_{54}N_2O_4$: C, 73.02; H, 10.03; N, 5.16; O, 11.79; 3 OCH_3, 17.18. Found: C, 72.37; H, 9.88; N, 5.49; O, 11.53; OCH_3, 15.38.

The second stage Hofmann degradation was carried out with 1.21 g. of crystalline reduced methine XVI and was performed exactly as described above (XIIIb → XV).

(40) *Cf.* N. D. Cheronis, "Micro and Semimicro Methods" in A. Weissberger's "Technique of Organic Chemistry," Vol. VI, Interscience Publishers, Inc., New York, N. Y., 1954, pp. 275–276.

(41) *Cf.* J. Weinstock and V. Boekelheide, THIS JOURNAL, **75**, 2546 (1953).

(42) Excessive handling of this substance was avoided since it was noted by R. Mirza in this Laboratory in some preliminary abortive experiments that heating with methanol during attempted recrystallization yielded some tetramethylammonium iodide (m.p. 228°).

Elimination of trimethylamine proceeded smoothly as demonstrated by the isolation of 0.45 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 XVII since treatment with one equivalent of ozone in ethyl acetate solution at −60° by the inverse technique[43] (which worked satisfactorily in a model experiment with isoeugenol methyl ether) followed by decomposition of the ozonide with zinc in acetic acid (24 hr., room temperature) yielded only 3% of isobutyraldehyde 2,4-dinitrophenylhydrazone after chromatography on bentonite–kieselguhr.[44] Careful examination of the non-volatile portion including chromatography did not yield any of the desired aldehyde XVIII[24] even though seed crystals of authentic dialdehyde (derived from an intermediate[23] 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° at 0.005 mm.) sample (no infrared hydroxyl absorption) appeared to be the diethyl ether XIX arising by solvolysis.

Anal. Calcd. for $C_{33}H_{52}O_6$: C, 72.75; H, 9.62; O, 17.62. Found: C, 73.24; H, 9.39; O, 17.04.

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 90 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 (deactivated 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 ethanol gave 0.53 g. (29%) of the picrate of **1-isobutyl-2-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (IVd)**, m.p. 152–153°, undepressed when mixed with a sample of the synthetic[18] picrate. Identity was confirmed by converting a portion of the picrate by the above-described ion-exchange method to the free base and comparing its infrared spectrum with that of the synthetic base.

Anal. Calcd. for $C_{21}H_{26}N_4O_8$: C, 54.54; H, 5.67. Found: C, 54.21; H, 5.90.

Fractions 47–83 were eluted with mixtures ranging from 1:1 hexane–benzene to 99:1 benzene–ether and after treatment with ethanolic picric acid solution, yielded 0.196 g. (10%) of **1-isobutyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IVb) picrate**, m.p. 183–185°. Identity was established by mixture melting point determination of the picrates as well as by infrared comparison of the synthetic[17] and natural bases (regenerated from its picrate by the ion exchange method).

Fractions 100–112, eluted with 9:1 benzene–ether, furnished only with great difficulty a picrate (10% yield, m.p. 150–155°) which on the basis of its analysis, kryptophenolic behavior and identification of its methylation product (see below) must be **1-isobutyl-2-methyl-6,7-dimethoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline (XXa) picrate.**

(43) *Cf.* P. Bladon, H. B. Henbest, E. R. H. Jones, G. W. Wood and G. F. Woods, *J. Chem. Soc.*, 4890 (1956).

(44) J. A. Elvidge and M. Whalley, *Chemistry & Industry*, 589 (1955).

Anal. Calcd. for $C_{22}H_{28}N_4O_{10}$: C, 51.96; H, 5.55; N, 11.02; 2 OCH_3, 12.20. Found: C, 51.51; H, 5.69; N, 11.05; OCH_3, 11.98.

A 73-mg. sample of the above base XXa, regenerated from its picrate by the ion exchange procedure, was methylated for 10 days at 0° with diazomethane in ether–methanol. The product was converted into its crystalline picrate, m.p. 132–134°, which proved to be identical by mixture melting point determination and infrared comparison of the respective free bases with a synthetic[18] specimen of **1-isobutyl-2-methyl-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline (XXb).**

Fractions 112–114 were eluted with ether and with 9:1 ether–methanol. The picrate of the residue melting unsharply above 210° could not be resolved into a pure component; it may represent dimeric material.

The phenolic, basic cleavage products (0.67 g.) were methylated with diazomethane in ether–methanol for 8 days in the refrigerator. The crystalline picrate (0.43 g., 23% yield, m.p. 181–184°) of **1-isobutyl-2-methyl-6,7-dimethoxytetrahydroisoquinoline (IVb)** could be separated directly without having to resort to chromatography, and identity with synthetic material[17] was established in the usual manner.

Anal. Calcd. for $C_{22}H_{28}N_4O_9$: C, 53.65; H, 5.73; N, 11.38; 2 OCH_3, 12.60; N-CH_3, 3.05. Found: C, 54.17; H, 5.67; N, 11.74; OCH_3, 12.51; N-CH_3, 3.20.

The mother liquors from the above picrate preparation were transformed into the free amine by the ion exchange method and then chromatographed on deactivated alumina leading to 0.164 g. of an oil. Treatment with picric acid furnished 0.175 g. (9%) of the picrate of **1-isobutyl-2-methyl-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline (XXb)**, thus raising the total yield of the trioxygenated cleavage product XXa to 19%.

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 0.576 g. (32%) of **1-isobutyl-2-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (IVd) picrate**, m.p. 151–153°, 0.227 g. (11.5%) of **1-isobutyl-2-methyl-6-methoxy-7-ethoxy-1,2,3,4-tetrahydroisoquinoline (IVc) picrate**, m.p. 152–153°, and 0.244 g. (12%) of **1-isobutyl-2-methyl-6-methoxy-7-ethoxy-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.[18] The structure of the third compound follows from its analysis, the presence of a free hydroxyl band in the infrared spectrum of the free base and from the constitution of pilocereine itself.

Anal. Calcd. for $C_{23}H_{30}N_4O_{10}$: C, 52.87; H, 5.79; N, 10.72; O, 30.62. Found: C, 52.67; H, 5.99; N, 10.54; O, 30.35.

Methylation of the phenolic, basic cleavage fraction (0.51 g.) in the standard manner and treatment with picric acid gave 0.356 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[17] sample.

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