Alkaloids of *Cassia* Species. I. Cassine[1]

R. J. HIGHET

Section on Chemistry, Laboratory of Metabolism, National Heart Institute, National Institutes of Health, Bethesda 14, Maryland

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A crystalline alkaloid, $C_{19}H_{37}NO_2$, has been isolated from *Cassia excelsa* Shrad. and named cassine. The functional groups are identified as a hydroxyl group, a secondary amine, and a methyl ketone. Dehydrogenation of cassine produces a 2,6-dialkyl-3-hydroxypyridine, and cleavage of ketone VI by a second-order Beckmann rearrangement demonstrates the 2-alkyl group to be methyl. These observations and deductions from the n.m.r. spectrum show III to be the structure of cassine.

The presence of alkaloids in the American tropical legume *Cassia excelsa* Shrad. has been noted by investigators of the U. S. Department of Agriculture,[2] and an alkaloid characterized by crystalline salts has been isolated by Brazilian workers.[3]

Extracting the leaves and twigs of *C. excelsa*[4] by conventional procedures yields a mixture of basic materials amounting to 2.9% of the dry weight. A fraction of this proved to be soluble in hot hexane; concentrating the solutions under reduced pressure left a clear oil. An ethanolic solution of this material was acidified by hydrochloric acid and crystallized to provide a mixture of hydrochlorides. Repeated chromatography of the free bases eventually produced pure samples of two alkaloids, cassine and casselsine. Selected fractions were recrystallized as the hydrochlorides and the pure bases regenerated and distilled.

Pure cassine melted at 57–58.5° and possessed a small but reproducible optical activity, $[\alpha]^{25}D$ −0.6°.[5] Analysis showed the empirical formula of $C_{19}H_{37}NO_2$, at least two C-methyl groups, no methoxyl groups, and an N-methyl group; this last result, however, was eventually shown to be spurious (following). The infrared spectrum showed carbonyl absorption (1720 cm.$^{-1}$) appropriate to a ketone, and a peak (3530 cm.$^{-1}$) in the NH or OH region. The CH stretching region was free of any absorption not attributable to aliphatic groups, and the compound showed no intense absorption in the ultraviolet region.

Acetylation of the base provided an O,N-diacetyl derivative as a neutral oil, $C_{23}H_{41}NO_4$, with infrared absorption at 1725 and 1630 cm.$^{-1}$, and without OH or NH peaks. Sodium borohydride reduced the base to a dihydro derivative, m.p. 53–57°. These derivatives and spectra identify the functional groups of the molecule as a secondary amine, a hydroxyl, and a ketone. Attempts to demonstrate the presence of a double bond failed. The molecule failed to absorb hydrogen when stirred with palladized charcoal, and the diacetyl derivative was not affected by potassium permanganate in acetone. Evidently cassine contains a cyclic system.

The n.m.r. spectrum of cassine (see Fig. 1) shows no protons with resonance at low field, and confirms the absence of aldehydic or olefinic protons. The peak at τ 6.55 corresponds to a single carbinol proton, showing the alcohol to be secondary. The peak at τ 7.95 might originate with a methyl ketone or an N-methyl group; the observations below demonstrate that the former possibility is correct. The only other methyl group visible is represented by a doublet centered at τ 8.98; it is, therefore, coupled with a single proton, and occurs in the group $>CHCH_3$.

Treating the base with hypoiodite solution produced iodoform and demonstrated the presence of a methyl ketone or carbinol. The ketone could be condensed with piperonal in the presence of alkali to give a piperonylidine ketone, m.p. 106–107.5°, $C_{27}H_{41}NO_4$, ν_{max} 1700 cm.$^{-1}$. Since a Kuhn–Roth determination on this product showed reduced C-methyl content, it seemed likely that cassine contained a methyl ketone, rather than a methyl carbinol. The peak at τ 7.95 in the n.m.r. spectrum and that at 1360 cm.$^{-1}$ in the infrared spectrum are consistent with this conclusion. In an attempt to condense the ketone with 2 moles of an aldehyde, cassine was heated in hydrochloric acid with benzaldehyde at 120° to produce a compound whose ultraviolet spectrum corresponds to the monobenzylidine derivative; no absorption at longer wave lengths characteristic of the bisbenzylidine derivative could be detected. This result implies branching at the α-carbon of the methyl ketone, which was substantiated by deuteration experiments. When cassine was equilibrated with deuteriomethanol in the presence of sodium methoxide, removed from the base, and re-equilibrated with water, the product contained 3.7 atoms of deuterium, consistent with the existence of a group, $-CHCOCH_3$.

When cassine was heated at 220° under nitrogen with palladized charcoal, it was converted to the optically inactive dehydro derivative, $C_{19}H_{31}NO_2$, m.p. 104–105°. This compound shows the characteristic ultraviolet spectra of a 3-hydroxypyridine[6] in neutral, acidic, and basic solutions, and retains the carbonyl absorption of the methyl ketone. The n.m.r. spectrum confirms the retention of the methyl ketone, and shows

(1) Presented at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962.

(2) M. E. Wall, C. R. Eddy, J. J. Wallaman, D. S. Correll, B. G. Schubert, and H. S. Gentry, "Steroidal Sapogenins. XXVI," ARS-73-4, U. S. Department of Agriculture, Philadelphia, Pa., 1954.

(3) O. Goncalves de Lima, I. L. d'Albuquerque, M. P. Machado, and G. P. Pinto, *Rev. Inst. Antibiot. Univ. Recife*, **1**, 23 (1958); *Chem. Abstr.*, **53**, 22212 (1959). This material, named cassilisin, formed a hydrochloride of m.p. 155.8–157.5° and a hydrosulfate of m.p. 271°. It has not been encountered in this study.

(4) The author is indebted to Dr. Quentin Jones of the U. S. Department of Agriculture Plant Introduction Station, Beltsville, Md., for supplying this material from the department's garden in Miami, Fla.

(5) Because the optical activity of the parent alkaloid is very small, the possibility must be considered that the activity arises from an impurity. However, N-methylcassine has a considerably greater activity ($[\alpha]D$ 6.5°) and the methiodide yet more ($[\alpha]D$ 15.8°). It seems unlikely that an impurity could be retained in these transformations to the extent these values imply.

(6) 3-Hydroxypyridines are unusual among phenols in showing a bathochromic shift in both acid and base. In particular, this phenomenon is not exhibited by 2- and 4-hydroxypyridines; *cf.* H. S. Mosher, "Heterocyclic Compounds," Vol. I, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1950, p. 442.

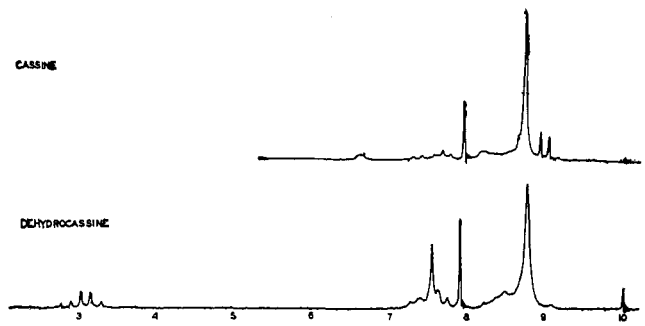
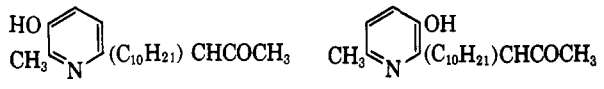


Figure 1.

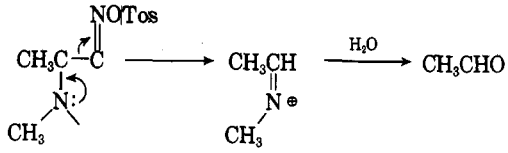
a new peak at τ 7.50 corresponding to an aromatic methyl group. As the doublet at τ 8.98 is absent, it is clear that dehydrogenation has converted a methylpiperidine into the corresponding methylpyridine. At low field the spectrum shows a quartet of two protons, β and γ on the pyridine ring. Thus the dehydrogenation product must be represented by one of the two alternative structures, Ia or Ib.



Ia Ib

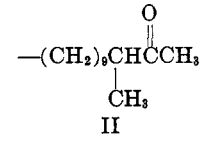
Analysis of cassine had shown the presence of an N-methyl group, and the n.m.r. spectrum with a peak at τ 7.95 is not inconsistent with this. However, the ready dehydrogenation to a pyridine without loss of a carbon atom, nor loss of the τ 7.95 peak in the n.m.r. spectrum, renders the presence of an N-methyl group in the original base impossible.[7] This conclusion was confirmed by a study of N-methyl derivatives of cassine. Treatment of cassine with methyl iodide or under Eschweiler–Clark conditions provided only impure products or starting material, but the base could be converted to the tertiary N-methyl derivative, $C_{20}H_{39}NO_2$, by stirring an ethanolic solution of the base and formaldehyde under hydrogen, in the presence of palladized charcoal. The oily N-methyl derivative formed a crystalline hydrochloride, m.p. 110–111°, $[\alpha]^{26}D$ 6.5°, and a methiodide, m.p. 91–93°, $[\alpha]^{26}D$ 15.8°, whose analyses showed but one and two N-methyl groups, respectively.

A method was now sought to reveal the substituent at the α-position of the piperidine ring between the hydroxyl group and the nitrogen atom of cassine by cleaving the molecule to recognizable products. When treatment by sodium periodate and by lead tetraacetate failed to effect a cleavage, a second-order Beckmann rearrangement was chosen, for recent studies[8] have shown this to be an effective method of cleaving α-amino oximes. The existing carbonyl group was eliminated by a Wolff–Kishner reduction of N-methylcassine to produce a base which formed a crystalline hydrochloride, m.p. 127–129°. Chromic acid oxidation of the material provided a ketone, isolated as the crystalline oxime, m.p. 166–168°, which was treated by pyridine and *p*-toluenesulfonyl chloride and the mixture refluxed with water to produce acetaldehyde, identified as its dinitrophenylhydrazone by paper chromatography in two systems. The α-amino oxime must, therefore, bear a methyl group to produce the acetaldehyde.



Structure Ia can now be recognized as the correct alternative.

The structure of the side chain may be inferred from the following arguments. (1) The methylene group α to the ketone has been shown to be substituted, and the empirical formula precludes a ring structure. (2) The side chain is, therefore, branched and dehydrocassine must possess an asymmetric center. However, dehydrocassine is optically inactive. It is most likely, then, that the branching is α to the ketone or to the piperidine ring, for such centers might well be racemized under dehydrogenation conditions. (3) The n.m.r. spectrum of cassine shows no methyl group other than the group on the ring and that of the ketone. Any other methyl groups must be obscured by the strong peaks of the methylene resonance. To possess a chemical shift near τ 8.7 the methyl protons must be β to an unsaturated group or a hetero atom. The only such position common to cassine and dehydrocassine is α to the ketone, and the side chain most likely possesses the structure II,[9] and cassine is III. The product of dehydrogenation must be represented by IV, while V and VI represent the Wolff–Kishner product and its oxidation product.



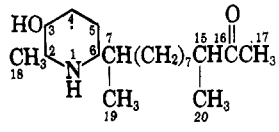
II

Recently, Tichy and Sicher have demonstrated that the stereochemistry of 2,6-dialkyl-3-hydroxypiperidine systems is reflected in the infrared spectrum by the OH

(7) Analysis of 3-hydroxypiperidine itself under standard conditions produced an N-methyl value of 5% ($C_5H_{11}NO$ would require 15%).

(8) *Cf.* (a) M. F. Bartlett, D. F. Dickel, and W. I. Taylor, *J. Am. Chem. Soc.*, **80**, 126 (1958); (b) R. K. Hill and R. T. Conley, *ibid.*, **82**, 645 (1960); (c) C. A. Grob, H. P. Fischer, N. Link, and E. Renk, *Helv. Chim. Acta*, **46**, 1190 (1963).

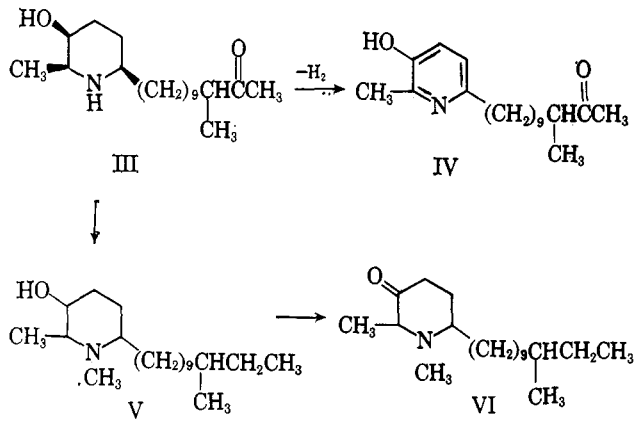
(9) In particular, the n.m.r. spectrum eliminates the possibility of *gem*-dimethyl groups, which would produce an unmistakable sharp peak at high field. The possibility of a methyl group β to the nitrogen, such as at C-19 in structure i, might be supported by the following arguments. A methyl group α to a nitrogen atom (*i.e.*, C-18), as well as that α to a carbonyl group (C-20) may well be obscured by the broad methylene peak,



i

the methyl doublet arising from the methyl group β to the nitrogen (C-19). In dehydrocassine, the ring methyl (C-18) produces the peak at τ 7.50 while the methyl groups α to the carbonyl (C-20) and α to the aromatic system (C-19) are obscured. Both asymmetric centers (C-7 and C-15) are capable of racemization during dehydrogenation. However, the possibility of a C-19 methyl may be excluded, since the chemical shift of a methyl group β to a nitrogen atom is actually near τ 8.9–9.0[10] and C-19 of i could not be obscured by the methylene resonance.

(10) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, Spectra No. 92, 296, and 302.



stretching frequency.[11a] In the all-*cis* systems, the most favorable configuration possesses the hydroxy group in the axial configuration (*cf.* VII) favorable to hydrogen bonding. As a result, the hydroxyl absorbs at a single frequency, about 100 cm.$^{-1}$ below the characteristic absorption of secondary hydroxyls, 3630 cm.$^{-1}$. Other configurations show absorption from both free and hydrogen-bonded hydroxyl. The sole peak from the hydroxyl of N-methylcassine occurs at 3530 cm.$^{-1}$, and that of the Wolff–Kishner product (V) appears at 3535 cm.$^{-1}$, revealing the all-*cis* configuration. The stereochemistry of cassine, then, is that represented by III or its mirror image.

Derivatives of 3-hydroxypiperidines occur rather seldom in nature, but cassine is obviously closely related to carpaine (VIII). The stereochemistry of carpaine has been demonstrated to be all-*cis* also.[11] The carbon skeleton of cassine contains the straight fourteen-carbon system of carpaine, with the addition of the group C–C–C–C. It seems reasonable to speculate that the former system arises in nature from the condensation of acetic acid units and the latter from a mevalonic unit.[11b]

Experimental[12]

Isolation.—Leaves of *Cassia excelsa* Shrad. (2.8 kg.) were extracted with 24 l. of 1% ethanolic tartaric acid at 50–60°. The extracts were filtered and concentrated under reduced pressure to 3 l., diluted with 6 l. of water, and treated with 300 ml. of 2 *N* sulfuric acid. The acid solution was filtered, washed with trichloroethylene, and made basic with ammonia. This solution was extracted with chloroform and the organic layers distilled to dryness to leave 81.3 g., 2.9%. For more convenient handling this material was dissolved in ethanol and diluted to 150 ml.

A 50-ml. aliquot of this solution, corresponding to 27 g. of the crude extract, was diluted to 300 ml. with 1 *N* hydrochloric acid and extracted twice with benzene. The aqueous solution was made basic by 25 ml. of 50% sodium hydroxide solution and extracted three times with chloroform; the extracts were washed with water and concentrated to dryness to leave a residue of 19.6 g. This was digested repeatedly with boiling hexane, leaving an insoluble residue of 6.5 g. The hexane solution was filtered and concentrated to dryness to yield 13.4 g. of a clear yellow oil. This material was dissolved in 100 ml. of ethanol and made acid by concentrated hydrochloric acid, diluted with 100 ml. of ethyl acetate, and scratched and chilled until a crystalline precipitate formed. Further crops could be obtained by concentrating the filtrates and adding ethyl acetate. Thus a total of 6.0 g. of crystalline hydrochlorides was obtained. The free base, obtained by dissolving the hydrochlorides in ethanol, diluting with chloroform, adding ammonia, and washing the organic phase with water, was chromatographed over 150 g. of silicic acid, eluting with chloroform with increasing concentration of methanol. The alkaloids were eluted chiefly by 3% and 5% methanol–chloroform solutions. Fractions were converted to hydrochlorides and identified by infrared spectra in Nujol. Casselsine appeared first and could be recognized by peaks at 1010 and 950 cm.$^{-1}$; cassine followed, showing peaks at 1012 and 990 cm.$^{-1}$. Material melting above 165° was collected as pure, the intermediate cuts being rechromatographed until pure materials were obtained. Thus, by repeated chromatography, 0.62 g. (0.06% of dry plant weight) of cassine hydrochloride and 0.56 g. (0.05%) of casselsine hydrochloride were obtained.[13]

Cassine hydrochloride crystallized from ethanol as clustered needles, m.p. 173–175°; ν_{max}^{nujol} 3290, 1715, 1530, 1170, 1160, 1010, and 990 cm.$^{-1}$; λ_{max} 276 mμ (ϵ 33). Repeated attempts to obtain satisfactory carbon analyses on carefully purified materials failed.

Anal. Calcd. for $C_{19}H_{38}NO_2Cl$: C, 65.60; H, 11.03; neut. equiv., 347.9. Found: C, 64.83, 64.87; H, 10.91, 10.84; neut. equiv., 349, 351.

Cassine was obtained by treating an aqueous suspension of the hydrochloride with ammonia and extracting with chloroform. Analytical material was obtained by distillation at 90° (0.001 mm.), m.p. 57–58°, unchanged by further chromatography; $[\alpha]^{25}_{589}$ −0.6°, $[\alpha]^{25}_{436}$ −1.7°, $[\alpha]^{25}_{380}$ −3.0° (*c* 8.0); $\nu_{max}^{CCl_4}$ 3530, 2930, 2860, 2810 (sh), 1720, 1360, and 690 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{37}NO_2$: C, 73.26; H, 11.97; N–CH_3, 4.85; C–CH_3, 9.64 for two; neut. equiv., 311.5. Found: C, 73.37, 73.34; H, 11.76, 11.84; N–CH_3, 2.99; C–CH_3, 8.70; neut. equiv., 306.

Cassine hydronitrate precipitated from dilute aqueous nitric acid and was recrystallized from ethyl acetate, m.p. 116–117°.

Anal. Calcd. for $C_{19}H_{38}N_2O_5$: C, 60.93; H, 10.23; N, 7.48. Found: C, 61.12; H, 9.91; N, 7.58.

Diacetyl Cassine.—Cassine (92 mg.) was heated with 10 ml. of acetic anhydride and 0.1 g. of sodium acetate on a steam bath for 1 hr., then added to 300 ml. of 1 *N* potassium bicarbonate, and stirred until no odor of the anhydride could be detected. The suspension was extracted with chloroform; the extract was washed with water, 1 *N* hydrochloric acid and water, and was distilled to dryness to leave a clear oil of 125 mg. This was chromatographed over silicic acid, eluting with chloroform. The center fractions of the eluate were distilled at 110° (0.002 mm.); ν_{max} 1725 (broad), 1630, and 1250 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{41}NO_4$: C, 69.83; H, 10.45. Found: C, 69.67; H, 10.61.

Piperonylidinecassine was prepared in a centrifuge tube by treating a solution of 157 mg. of cassine and 180 mg. of piperonal in 1 ml. of ethanol with 1 ml. of 6 *N* sodium hydroxide at room temperature. After 15 min., the solution was scratched and diluted with water until the product crystallized. It was centri-

(11)(a) M. Tichy and J. Sicher, *Tetrahedron Letters*, 511 (1962). (b) NOTE ADDED IN PROOF.—Mass spectrometric studies of cassine and dehydrocassine have shown no peaks of *m/e* values greater than 297 and 291, respectively; if these values represent the true molecular weights, structures III–VI must be altered by changing the number of methylene groups in the side chain from 9 to 8.

(12) All melting points were observed on a Kofler microscope hot stage and are corrected. The author is indebted to Mrs. K. S. Warren for polarimetric and spectrophotometric data and to Mr. David Rogerson for extractions of plant material. Rotations were measured in ethanolic solution on a Rudolph photoelectric spectropolarimeter with a 1-dm. tube. Ultraviolet spectra were recorded in absolute ethanol on a Cary Model 11 MS recording spectrophotometer. Infrared spectra were observed either on a Perkin-Elmer Model 21 or a Beckmann IR-7 double-beam spectrophotometer in chloroform solution, unless otherwise specified. We are indebted to Dr. E. D. Becker and Mr. R. B. Bradley of the National Institute of Arthritis and Metabolic Diseases for the n.m.r. spectra, which were obtained on a Varian-V-4300-2 n.m.r. spectrometer operating at 60 Mc. Frequencies were obtained relative to tetramethylsilane as an internal standard by interpolation using the audio side-band technique. Analyses were performed by W. Manser of Zurich, Switzerland, by J. F. Alicino of Metuchen, N. J., and by Micro-Tech Laboratories of Skokie, Ill.

(13) The characterization of casselsine will be described in a later publication.

fuged and the precipitate dried and crystallized from ethyl acetate to yield 101 mg. of m.p. 97–101°. Several recrystallizations provided material of m.p. 106–107.5°; ν_{max}^{Nujol} 3350, 1700, 1620, 1600, 1035, 1000, and 630 cm.$^{-1}$; λ_{max} 247 mμ (ε 10,000), 297 (10,300), and 338 (18,800).

Anal. Calcd. for $C_{27}H_{41}NO_4$: C, 73.10; H, 9.32; C-CH_3, 3.39. Found: C, 72.63; H, 9.10; C-CH_3, 3.46.

Vigorous Condensation of Cassine with Benzaldehyde.—Cassine (6.1 mg.) was sealed in a tube with 27 mg. of benzaldehyde and 13.5 mg. of a 10% sodium hydroxide solution, and 0.2 ml. of ethanol, and heated 22 hr. at 120°. After cooling, the tube was opened, and the contents acidified with dilute hydrochloric acid and extracted with ether. The aqueous layer was made basic with ammonia and extracted with chloroform; the extract was washed with water and distilled to dryness to leave a residue of 6 mg. The ultraviolet spectrum showed only a peak at 287 mμ.

Tetradeuteriocassine was prepared by dissolving 9 mg. of cassine in 0.5 ml. of CH_3OD and treating with a drop of 0.1 *N* sodium methoxide in CH_3OD. After 30 min. the solution was distilled to dryness under reduced pressure, and the residue dissolved in ether, centrifuged, and the clear centrifugate distilled to dryness under reduced pressure. The infrared spectrum showed peaks at 2260, 2220 and 2180 cm.$^{-1}$, with minor changes about 1360 cm.$^{-1}$; m.p. 57–59°. The material was distilled at 100° (0.001 mm.).

Anal. Calcd. for $C_{19}H_{33}D_4NO_2$: 10.8% atom excess deuterium. Found: 9.91%.[14]

Dihydrocassine.—Cassine (112 mg.) was dissolved in 3 ml. of methanol and treated with 100 mg. of sodium borohydride in four portions. After the solution had stood 0.5 hr. it was made acid with hydrochloric acid, extracted twice with ether, made basic with 10% sodium hydroxide, and extracted twice with chloroform and twice with 4:1 chloroform–ethanol. The organic layers were concentrated to dryness and the residue acidified with hydrochloric acid and dried under reduced pressure, to leave 115 mg. of m.p. 161–170°. Recrystallization from ethanol–ethyl acetate gave material of m.p. 173–176°; admixture of cassine hydrochloride lowered the melting point to 168–173°. The infrared spectrum (potassium bromide) showed a sharp peak at 3400, broad absorption from 3000–2400 and no carbonyl absorption, and significant peaks at 1540, 1380, and 1000 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{40}NO_2Cl$: C, 65.20; H, 11.52; Cl, 10.13; neut. equiv., 350.5. Found: C, 64.97; H, 11.20; Cl, 10.57; neut. equiv., 346.

N-Methylcassine was prepared by stirring 0.415 g. of cassine, 117 mg. of 10% palladized charcoal, and 5 ml. of 30% formaldehyde in 30 ml. of ethanol under hydrogen for 4 hr. The solution absorbed 11 ml. of hydrogen. It was filtered, concentrated to 3 ml., diluted with water, and made acid with 6 *N* hydrochloric acid. This solution was extracted with ether, made basic with ammonia and extracted twice with chloroform; the extracts were washed with water and concentrated to dryness under reduced pressure. The residue (403 mg.) was converted to its hydrochloride by concentrated acid. Drying provided a residue of 470 mg. of material of m.p. 107.5–109.5°. Recrystallization from ethyl acetate produced material of m.p. 110.5–111.5°. The infrared spectrum resembled that of cassine hydrochloride, with increased absorption at 2700 cm.$^{-1}$, lacking the bands at 1530 and 1015 cm.$^{-1}$, but retaining those at 3290, 1720 and 988 cm.$^{-1}$; $[\alpha]^{26}_{589}$ 6.5°, $[\alpha]^{26}_{436}$ 14°, $[\alpha]^{26}_{350}$ 26° (*c* 0.92).

Anal. Calcd. for $C_{20}H_{40}NO_2Cl$: C, 66.36; H, 11.06; Cl, 9.80; NCH_3, 4.15; neut. equiv., 362. Found: C, 66.03; H, 11.43; Cl, 9.74; NCH_3, 4.34; neut. equiv., 363.

N-Methylcassine methiodide was prepared by allowing 230 mg. of N-methylcassine in ethanol solution to stand with 2 ml. of methyl iodide overnight. Evaporation of the solvents left a residue of 330 mg., which crystallized on trituration with ethyl acetate, m.p. 87–89°. Crystallization from the same solvent produced material of m.p. 91–93°; $[\alpha]^{26}_{589}$ 15.8°, $[\alpha]^{26}_{436}$ 31.4°, $[\alpha]^{26}_{380}$ 42.6°, $[\alpha]^{26}_{320}$ 69.7°, (*c* 1.015); ν_{max}^{KBr} 3330, 1710 and 990 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{42}NO_2I$: C, 53.96; H, 9.06; I, 27.14; NCH_3, 6.44 for two. Found: C, 54.06; H, 8.70; I, 26.9; NCH_3, 7.45.

Dehydrocassine.—Cassine (0.84 g.) was heated with 278 mg. of 10% palladized charcoal under nitrogen for 30 min. at 220°. The waxy product was dissolved in ethanol, centrifuged, and the supernatant diluted with water, acidified with hydrochloric acid, and extracted three times with benzene; the extract was washed with water and distilled to dryness under reduced pressure to leave a residue of 83 mg. The aqueous raffinate was made basic with ammonia and extracted twice with 4:1 chloroform–ethanol solution, which was washed with water and distilled to dryness under reduced pressure, leaving a residue of 577 mg. This was chromatographed over a column of silicic acid; eluting with 1% methanol in chloroform produced 297 mg. of dehydrocassine, m.p. 97°. Recrystallization from aqueous methanol provided material of m.p. 104–105°; $\nu_{max}^{CCl_4}$ 3611 cm.$^{-1}$; ν_{max}^{Nujol} 2600 (broad), 1722, 1590, 1508, 1285 and 833 cm.$^{-1}$; λ_{max} 224 mμ (ε 9180), 288 (6500); on addition of alkali the peaks shifted to 245 (12,600) and 311 (8600). An acid solution showed λ_{max} 230 mμ (ε 7450) and 301 (10,200). The material exhibited no optical activity between 589 and 370 mμ with a maximum $[\alpha] < 0.5°$ (*c* 1.02).

Anal. Calcd. for $C_{19}H_{31}NO_2$: C, 74.71; H, 10.23. Found: C, 74.35; H, 9.91; OCH_3, 0.0; N-CH_3, 0.0.

Wolff–Kishner Reduction of N-Methylcassine.—A 300-mg. sample of N-methylcassine, 175 mg. of potassium hydroxide, and 0.6 ml. of 85% hydrazine hydrate were warmed on a steam bath in 5 ml. of ethylene glycol for 1 hr. The flask was then provided with a downward condenser and the volatile components distilled to a temperature of 204°. The solution was refluxed 4 hr., cooled, diluted with water, made acid with dilute hydrochloric acid, and washed twice with ether. The aqueous layers were made basic by ammonia and extracted twice with chloroform, and the extracts were washed with water and concentrated under reduced pressure to a residue of 225 mg. This material was dissolved in ethanol, made acid by dilute hydrochloric acid, and concentrated to dryness. Crystallization from ethyl acetate provided 140 mg., m.p. 125–129°. Repeated crystallization provided material of m.p. 127–129°. The infrared spectrum showed no absorption between 1600 and 2000 cm.$^{-1}$; $[\alpha]^{24}D$ 9.0°, $[\alpha]^{24}_{456}$ 13.5°, $[\alpha]^{24}_{370}$ 18.5°, $[\alpha]^{24}_{300}$ 38° (*c* 0.54). In dilute carbon tetrachloride solution, the hydroxyl peak occurred at 3535 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{42}NOCl$: C, 69.02; H, 12.17. Found: C, 68.96; H, 12.26.

Oxidation and Cleavage.—The base regenerated from 150 mg. of the above salt was dissolved in acetone and treated with 0.21 ml. of Kiliani reagent[15] for 20 min. The solution was diluted with water, extracted twice with ether, made basic by ammonia, and extracted twice with chloroform; the extracts were washed with water and concentrated to dryness. The 48-mg. residue was converted to the oxime by warming with 100 mg. of hydroxylamine hydrochloride and dilute ammonia in ethanol. It was concentrated to dryness under reduced pressure and the residue crystallized from ethyl acetate and benzene to yield 29 mg., m.p. 164–167°.

A 7-mg. sample of this material was sealed in a test tube with 1 ml. of pyridine and 12 mg. of *p*-toluenesulfonyl chloride and the tube heated 3 hr. in a steam bath and 1 hr. at 130°. The tube was cooled, the contents treated with 1 ml. of water and refluxed 1 hr. The mixture was diluted with water, extracted twice with ether, and treated with a sulfuric acid solution of 2,4-dinitrophenylhydrazine. A precipitate formed which amounted to 5 mg. It was chromatographed on paper impregnated with dimethylformamide. Elution by cyclohexane gave an R_f value of 0.39, identical with that of known acetaldehyde dinitrophenylhydrazone. The derivative of acetone had an R_f value of 0.54 when run simultaneously.[16] On untreated paper, eluting by methanol–saturated heptane,[17] the precipitate and known acetaldehyde dinitrophenylhydrazone had an R_f value of 0.43; acetone dinitrophenylhydrazone, R_f 0.61.

Iodoform Test.—Cassine (14 mg.) was dissolved in 0.5 ml. of purified dioxane and treated with 0.1 ml. of 10% sodium hydroxide and 0.35 ml. of *ca.* 1 *N* iodine solution in 20% potassium iodide, and heated at 60° for 2 min.[18] Filtering the precipitate provided 1.7 mg. of iodoform, m.p. 120–122°, undepressed by admixture of authentic material.

(14) Performed by Mr. Joseph Nemeth, Urbana, Ill.

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