6.60 (s, 1 H), 6.81 (d, J = 8 Hz, 2 H), 7.06 (d, J = 8 Hz, 2 H); mass spectrum m/e (rel intensity) 333 (M^+ <1), 332 (1), 209 (100), 124 (13).

The oxalate of **9** crystallized from ethanol–ether as colorless needles, mp 127–129°, $[\alpha]_D$ −93° (c 0.14). An authentic sample of (*S*)-*O*,*O*-bis(deuteriomethyl)-*N*-methylcoclaurine was prepared by deuteriomethylation of (*S*)-*N*-methylcoclaurine. Its oxalate crystallized from ethanol–ether as needles, mp 128–129°, $[\alpha]_D$ +101° (c 0.1), and it was found to be identical (ir, mixture melting point, TLC) with the oxalate of **9**.

From the phenolic fraction, **10** was isolated by PLC as an oil: $[\alpha]_D$ −36° (c 0.05); NMR δ 2.42 (s, 3 H, 1 NMe), 3.77 (s, 3 H, 1 OMe), 5.90 (br, 2 H, 2 OH), 6.52 (s, 1 H), 6.29 (s, 1 H), 6.60 (d, J = 8 Hz, 2 H), 6.90 (d, J = 8 Hz, 2 H); mass spectrum m/e (rel intensity) 299 (M^+, 1), 192 (100), 107 (9). The ir ($CHCl_3$) and NMR spectra of **10** were identical with those of an authentic sample of its enantiomer.

A portion of the phenolic fraction (20 mg) was treated with ethereal diazoethane. Work-up in the usual manner after 2 days yielded *O*,*O*′-diethyl-*N*-methylcoclaurine (**11**, 17 mg) as a pale yellow oil. It was converted to the oxalate which crystallized from ethanol–ether as needles: mp 172–174°; $[\alpha]_D$ −114° (c 0.05) (lit.[11] mp 173–174°, $[\alpha]_D$ −123°); mass spectrum m/e (rel intensity) 355 (M^+, 1), 220 (100), 135 (11). The ir spectrum, mixture melting point, optical rotation, and R_f of this compound were identical with those of an authentic sample.

N-Methylation of Daphnoline (3). To a methanol–chloroform solution of daphnoline (**3**, 13 mg), excess of 40% formaldehyde solution was added, and the mixture was stirred at room temperature for 2 hr.

The solution was then cooled in an ice bath and $NaBH_4$ was added in small portions. The solution was further stirred for 1 hr. Work-up as usual gave 13 mg of a transparent oil which crystallized from chloroform as colorless prisms, mp 182–183°, identical (ir, mixture melting point, TLC) with aromoline (**1**).

Acknowledgment. We thank the National Institutes of Health for a grant (CA-11445) in support of this work, and also the Fundación Juan March for the supporting fellowship to one of us (J. M. Saá). We also thank the following individuals for their invaluable assistance: B. A. Krukoff (Honorary Curator of New York Botanical Garden and Consulting Botanist of the Merck Sharp and Dohme Research Laboratories) for the supply of plant material, identification of the voucher sample, and botanical consultation; Drs. I. R. C. Bick (University of Tasmania), M. Tomita (University of Kyoto), and J. R. Boissier (Division Scientifique Roussel Uclaf) for authentic samples of daphnoline, homoaromoline, and phaeanthine, respectively; Drs. C. Hignite and C. Costello (Massachusetts Institute of Technology) for the determination of high-resolution mass spectra.

Registry No. —**1**, 519-53-9; **2**, 17132-74-0; **3**, 479-36-7; **4**, 57377-42-1; **5**, 1263-79-2; **6**, 57288-11-6; **9**, 57256-00-5; **9** oxalate, 57256-01-6; **10**, 5096-70-8; **11**, 6681-71-6.

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β-Phenethylamine and Tetrahydroisoquinoline Alkaloids from the Mexican Cactus *Dolichothele longimamma*[1]

Richard L. Ranieri and Jerry L. McLaughlin*

Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907

Received July 28, 1975

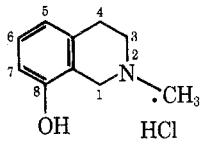
Seven crystalline alkaloids have been isolated and identified from extracts of a Mexican "peyote" cactus, *Dolichothele longimamma* (DC.) Br. and R. Five of these are new alkaloids: *N*-methyl-β-hydroxy-4-methoxy-β-phenethylamine (longimammine or 4-*O*-methylsynephrine), 6-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (longimammosine), 8-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (longimammidine), 6-methoxy-1,2,3,4-tetrahydroisoquinoline (longimammatine), and 4,8-dihydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (longimammamine). Although these compounds have all previously been synthesized, a new and convenient route is described for the syntheses of longimammidine and longimammosine. The known cactus alkaloids, (−)-normacromerine and (±)-synephrine, were also found in this species.

The peyote cactus, *Lophophora williamsii* (Lem.) Coult., has a well-documented history as a folkloric medicine and is known to contain many β-phenethylamine and tetrahydroisoquinoline alkaloids including the hallucinogen, mescaline.[2] Several ethnobotanical reports by Schultes suggest that *Dolichothele longimamma* (DC.) Br. and R., another Mexican "peyote" cactus, may cause similar psychoactive effects.[3] Early reports state that this genus contains unknown poisonous alkaloids,[4] and in a recent TLC screen of some *Dolichothele* species several new unidentified cactus alkaloids were detected in *D. longimamma*.[5] In the present communication we report the isolation and structure determination of seven alkaloids from this cactus.

TLC visualization[1a,6] of alkaloid-bearing fractions[5] from freeze-dried and pulverized *D. longimamma* confirmed the presence of several compounds that were distinct from previously known cactus alkaloids.[6,7] Large-scale extraction, involving basification of the plant material, chloroform ma-

cerations, acid–base partitioning, and anion-exchange chromatography, yielded three fractions consisting of the water-soluble, the nonphenolic, and the phenolic alkaloids. Separation of the alkaloids in these fractions was achieved by preparative TLC using silica gel as the adsorbent.

Three new tetrahydroisoquinolines (**1–3**) and a known β-phenethylamine, synephrine (**4**), were crystallized from the phenolic fraction. The structure determinations of compounds **1–3** were based primarily on their ^{1}H NMR and mass spectra; synephrine was identified by TLC.



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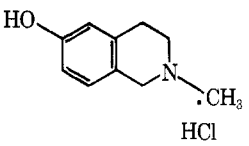

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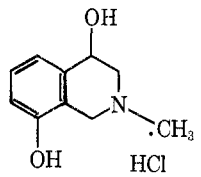

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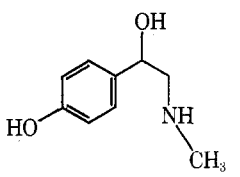

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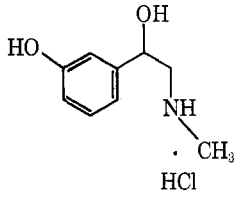
The mass spectrum of compound **1** exhibited a high-intensity molecular ion peak corresponding to $C_{10}H_{13}NO$ (*m/e* 163). An intense peak at *m/e* 120 (M − 43), due to a retro-Diels–Alder reaction[8] of the molecular ion, strongly suggested a tetrahydroisoquinoline structure. The ^{1}H NMR spectrum displayed a three-proton singlet at δ 3.08 attributable to the *N*-methyl protons and a four-proton multiplet centered at δ 3.45 corresponding to the C-3,4 ethylene protons. A two-proton AB pattern centered at δ 4.29 (J = 16 Hz) was assigned to the C-1 protons.[9] The aromatic region showed a one-proton triplet centered at δ 7.25 (J_o = 8 Hz) and a two-proton doublet (two overlapping doublets) centered at δ 6.85 (J_o = 8 Hz); similar ^{1}H NMR patterns have been observed for other tetrahydroisoquinoline hydrochlorides that are monosubstituted on the aromatic ring.[10] An aromatic pattern of a triplet and doublets, as observed for compound **1**, is characteristic of C-5 and C-8 oxygenated tetrahydroisoquinoline hydrochlorides and serves to distinguish these compounds from their C-6 and C-7 oxygenated isomers, which exhibit an aromatic pattern of two doublets and a doublet of doublets.[10] A C-8 hydroxyl explains the relatively large difference in chemical shifts (53 Hz) between the A and B protons of C-1.[9]

The essentially identical mass spectra of compounds **1** and **2** (longimammosine hydrochloride) indicated an isomeric relationship between these two alkaloids involving, perhaps, an alternative positioning of the hydroxyl at C-5, C-6, or C-7. The ^{1}H NMR spectra of **1** and **2** were quite similar except for the aromatic absorption patterns. In the aromatic region **2** exhibited a one-proton doublet centered at δ 7.10 (J_o = 8 Hz), a doublet of doublets (J_o = 8, J_m = 2.5 Hz), partially resolved and centered at δ 6.82, and an unresolved doublet (meta coupling) centered at δ 6.77. This pattern is indicative of a C-6 or C-7 hydroxyl,[10] but the exact positioning was not proven to be at C-6 until **2** was synthesized.

Compound **3** (longimammamine hydrochloride) was optically active ($[\alpha]^{25}$D −60°) indicating asymmetry. The mass spectrum exhibited a molecular ion corresponding to $C_{10}H_{13}NO_2$ (*m/e* 179). An intense peak at *m/e* 136 (*M* − 43) indicated a retro-Diels–Alder reaction, again implicating a tetrahydroisoquinoline.[8] A peak attributable to a loss of hydrogen and water was observed at *m/e* 160 (*M* − 19) and hinted that a C-4 hydroxyl might be present. Such 4-hydroxytetrahydroisoquinolines would not be unexpected in nature; biosynthetically they could arise from cyclization of β-hydroxy-β-phenethylamines, such as synephrine and normacromerine, which are not uncommon in cacti.[5,7,11]

The ^{1}H NMR spectrum of **3** exhibited a one-proton triplet at δ 5.07 (J = 3 Hz) due to the C-4 proton and a broad two-proton singlet at δ 3.60 attributable to the C-3 protons. Previous reports[12] describing the ^{1}H NMR spectra of simple 4-hydroxytetrahydroisoquinolines containing oxygenated substituents on the aromatic ring describe similar absorption values for the C-3 and C-4 protons. A singlet at δ 3.12 corresponded to the three *N*-methyl protons. An aromatic pattern of two doublets of one proton each centered at δ 7.04 and 6.92 (J_o = 8 Hz) and a one-proton triplet at δ 7.32 (J_o = 8 Hz) implicated a C-5 or C-8 hydroxyl on the benzene ring. A two-proton AB pattern, due to the C-1 protons, centered at δ 4.34 (J = 16 Hz), in which the chemical shift difference between the A and B protons is of the same order of magnitude (41 Hz) as the C-1 protons in compound **1**, indicated that **3** also possessed an 8-hydroxy function.

Recently, the Pictet–Spengler synthesis of tetrahydroisoquinolines has been applied to the reaction of phenylephrine (**5**) with formaldehyde; this reaction has yielded two isomeric compounds, **6** and **3**, the respective products of para and ortho ring closure of **5**.[13] We employed this reaction starting with L-phenylephrine, to obtain **6** and **3**. The synthesized **3** exhibited $[\alpha]^{25}$D −40°, indicating some racemization when compared with the natural compound ($[\alpha]^{25}$D −60°). Bobbitt et al.[12a,14] have hydrogenolyzed a series of 4-hydroxytetrahydroisoquinoline hydrochlorides to the corresponding tetrahydroisoquinoline hydrochlorides. We used this reaction to obtain **1** and **2** from **3** and **6**, respectively. The combination of these two reactions represents a new and convenient route to **1** and **2**. The synthetic **1**, **2**, and **3** exhibited physical and spectral properties indistinguishable from those of the compounds isolated from the phenolic fraction of *D. longimamma* and served to verify the correctness of the proposed structures.



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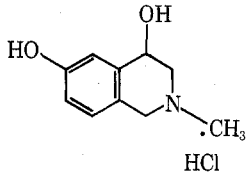

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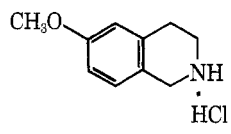
Compound **4** (synephrine) was identified initially by chromatographic comparisons with reference (±)-synephrine. The isolated alkaloid exhibited no optical rotation at the sodium D line. Spectral, physical, and TLC comparisons of the isolate with reference (±)-synephrine verified the identification. A larger quantity (1.5 g) of (±)-synephrine was isolated from the water-soluble fraction of the alkaloid extracts and was the only isolate obtained from this fraction. Synephrine represented the major alkaloid of this cactus species.

Three crystalline alkaloid hydrochlorides, compounds **7–9**, were isolated and identified from the nonphenolic alkaloid fraction.

Compound **7** (longimammatine hydrochloride) exhibited a high-intensity molecular ion in the mass spectrum corresponding to $C_{10}H_{13}NO$ (*m/e* 163). A high-intensity peak in the mass spectrum at *m/e* 134 (M − 29) again indicated a retro-Diels–Alder reaction and suggested that **7** was another tetrahydroisoquinoline. The ^{1}H NMR spectrum showed a two-proton singlet at δ 4.30 attributable to the C-1 protons. A three-proton singlet at δ 3.81 indicated a methoxy



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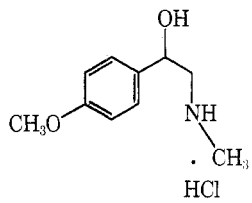

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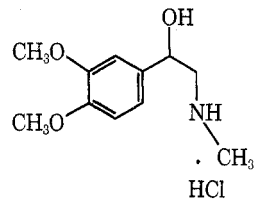

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substituent on the benzene ring. An A_2X_2 pattern of two triplets of two protons each was observed at δ 3.50 and 3.09 (J = 6 Hz) and was assigned to the C-3 and C-4 protons, respectively. A three-proton aromatic pattern similar to that observed for compound 2 indicated that the methoxy substituent was likely at C-6. A Pictet–Spengler synthesis of 7 from m-methoxy-β-phenethylamine was performed by a method analogous to one used by Helfer.[15] The physical and spectral properties of the synthetic compound and the isolated 7 were essentially identical.

Compound 8 (longimammine hydrochloride or 4-O-methylsynephrine) was optically active ($[\alpha]^{25}D$ −36°) indicating asymmetry. A low-intensity molecular ion peak corresponding to $C_{10}H_{15}NO_2$ (m/e 181) was present in the mass spectrum and a base peak at m/e 44 and an intense peak at m/e 137 (M − 44) indicated an N-methyl-β-phenethylamine. In the ^1H NMR spectrum a three-proton singlet at δ 2.77 confirmed the presence of an N-methyl group. An A_2X pattern of a two-proton doublet (J = 7 Hz) centered at δ 3.29 and a one-proton triplet (J = 7 Hz) centered at δ 5.01 indicated a β-hydroxy substituent. A four-proton A_2B_2 aromatic pattern centered at δ 7.21 suggested para substitution on the benzene ring, and a three-proton singlet at δ 3.83 indicated that this para substituent was a methoxy group. Racemic 8 was synthesized via a Houben–Hoesch condensation followed by sodium borohydride reduction.[16] ^1H NMR and mass spectra of the synthetic and isolated 8 were essentially identical. In addition, the synthetic and isolated compounds consistently cochromatographed in TLC.

Compound 9 was also optically active ($[\alpha]^{25}D$ −60.6°). The ^1H NMR and mass spectral data indicated that this compound was (−)-N-methyl-3,4-dimethoxy-β-hydroxy-β-phenethylamine (normacromerine). This identification was confirmed by mixture melting point comparisons, cochromatography, and essentially identical ir spectra of the isolated compound 9 and reference (−)-normacromerine hydrochloride.[16a]

Compounds 1 (longimammidine hydrochloride), 2 (longimammosine hydrochloride), 3 (longimammamine hydrochloride), 7 (longimammatine hydrochloride), and 8 (longimammine) have never before been isolated from nature and represent new cactus alkaloids; their syntheses have been previously reported.[10,13a,15,16] Synephrine and normacromerine are previously known as cactus alkaloids.[11] A single oxygenated substituent at C-6 or C-8 in compounds 1–3 and 7 are unusual for plant tetrahydroisoquinolines since tyrosine, the usual precursor, would only give rise to C-7 oxygenated derivatives.[9,17] These tetrahydroisoquinolines may be biosynthetically cyclized from meta tyramines; the aromatic substituents may be added by oxidations after cyclization of the phenethylamine has occurred; or the aromatic ring could represent Dopa which has been reduced at the para position. The origin of the 4-hydroxyl of compound 3 gives rise to additional biogenetic speculations. The biosynthesis of these new compounds as well as their possible psychoactive effect remains to be determined. Synephrine is a well-known sympathomimetic;[18] normacromerine produced no effects on the conditioned avoidance response in rats and is probably not psychoactive;[19] and (±)-N-methyl-4-methoxy-β-hydroxy-β-phenethylamine (3, longimammine) has recently been reported to have monoamine oxidase (MAO) inhibiting activity.[20] The co-occurrence of longimammine and synephrine could block the activity of MAO, potentiate the stimulant effects of synephrine, and possibly help to explain the folkloric uses of *D. longimamma* as a psychoactive "peyote" cactus.

Experimental Section

General Experimental. Melting points were determined on a Laboratory Apparatus Mel-Temp melting point apparatus and are uncorrected. Ultraviolet spectra were determined in 95% ethanol on a Cary Model 17 recording spectrophotometer. Infrared spectra were determined on a Beckman Model IR-33 recording spectrophotometer using KBr pellets. Proton magnetic resonance spectra were determined on a Jeol PFT-100 spectrometer or a Varian A-60 spectrometer using Me_4Si or DSS as internal standards. Mass spectra were determined on a Hitachi RMU-6 spectrometer with the sample being introduced by the direct insertion probe. Values of $[\alpha]D$ were determined on a Cary 60 recording spectropolarimeter. All hydrogenations were carried out on a Parr hydrogenation apparatus.

Analytical TLC plates were purchased from Baker (Baker-flex silica gel 1B or 1B2-F). Preparative TLC plates (20 × 20 cm) were prepared with a 1 mm layer of silica gel PF-254 (Brinkmann). Analytical separations and cochromatography were achieved by use of the following solvent systems:[11a] solvent A, ethyl acetate–methanol–58% ammonium hydroxide (17:2:1); solvent B, chloroform–ethanol–58% ammonium hydroxide (15:20:1); solvent E, diethyl ether–acetone–methanol–58% ammonium hydroxide (9:8:2:1); solvent F, diethyl ether–methanol–58% ammonium hydroxide (17:2:1); solvent G, chloroform–acetone–58% ammonium hydroxide (10:17:1). Fluorescamine,[1a] dansyl chloride,[6] iodoplatinate,[1a] and tetrazotized benzidine (TZB)[6] were used as the visualization reagents. Preparative scale isolations were achieved using solvent F with repeated developments. The degree of separation of the various bands on the TLC plates was monitored under short-wave uv light and by spraying the edge of each plate, when necessary, with dansyl chloride, followed by overspraying with TZB. The appropriate bands were scrapped from the plates, combined, and eluted with 5% ammonium hydroxide in ethanol.

***Dolichothele longimamma*. Extraction and Fractionation into Phenolic, Nonphenolic, and Water-Soluble Portions.** Freeze-dried, pulverized *D. longimamma* (354 g)[21] was placed in a Soxhlet extractor and continuously extracted with petroleum ether (bp 30–60°) for 24 hr to remove lipids (37 g, 10.5%). The defatted marc was basified with chloroform–methanol–58% ammonium hydroxide, 2:2:1, and extracted with a 1-l. solution of chloroform–methanol–ammonium hydroxide, 9:9:1, and by maceration with ten 1-l. portions of chloroform. The combined extracts were condensed under vacuum evaporation to give 50 ml of a thick black-brown syrup. This material was processed, essentially as previously described,[11c] to yield fractions A (alkaloids), B (nonalkaloidal materials), and C (water-soluble alkaloids). Fraction A was separated into phenolic and nonphenolic fractions using 70 g of the strongly basic ion-exchange resin, Amberlite IRA-401S in the hydroxide form, packed in a glass column (2 × 34.5 cm).[6]

Resolution and Identification of Phenolic Alkaloids. Spraying of an analytical TLC plate spotted with portions of the phenolic fraction and developed in solvent F showed six spots with the following R_f values 0.76, 0.67, 0.53, 0.41, 0.31, and 0.18. Preparative TLC (eight plates) was employed to give four crystalline compounds.

Compound 1, longimammidine hydrochloride, was isolated as the free base and had an R_f of 0.76. This compound, when chromatographed on a TLC plate, showed no visualization reaction with fluorescamine. Overspraying with dansyl chloride showed a yellow fluorescent spot, while a third spraying with iodoplatinate produced a purple spot. A second plate sprayed with TZB showed an orange spot. Recrystallization from ethanol gave 68 mg of brown crystals (mp 171–174°, lit.[10] mp 175.5–176°).

The hydrochloride 1 was prepared by the addition of 5% hydrochloric acid in ethanol to give 67 mg (0.0019% yield) of colorless crystals. Recrystallization from ethanol–ether gave 57 mg of crystals (mp 246–247°, lit.[10] mp 243–244°): uv max λ (ε) 279 (2100), 217 (6400); ^{1}H NMR (100 MHz, D_2O) δ 3.08 (3 H, s, NCH_3), 3.45 (4 H, m, 3-CH_2, 4-CH_2), 4.29 (2 H, 2d, J = 16 Hz, $\Delta\nu$ = 53 hz, 1-CH_2), 6.85 (2 H, d, J_o = 8 Hz, 5-CH, 7-CH), 7.25 (1 H, t, J_o = 8 Hz, 6-CH); low-resolution mass spectrum m/e (percent) 163 (M^+, 68), 162 (base peak), 120 (58), 91 (28), 44 (41); ir 3100, 1590, 1460, 1270, 990 cm^{-1}. A mixture melting point determination with the synthetic compound showed no depression. Cochromatography of the isolate with synthetic material showed identical mobilities in solvents A, B, E, F, and G. The ir spectra of the isolate and synthetic material were indistinguishable.

Longimammosine hydrochloride (2) was isolated as the free base (R_f 0.67, solvent F). This compound gave the same TLC visualization reactions with fluorescamine and dansyl chloride as did compound 1. A blue spot was observed on overspraying with iodoplatinate, and a yellow-brown spot formed with TZB. Recrystallization from ethanol gave 62 mg of the free base (mp 180–182°). Conversion to the hydrochloride gave 68 mg (0.0019% yield) of colorless crystals (mp 234–235°, lit.[22] mp 236°): uv max λ (ε) 286 (1700), 228 (6200), and 221 (6600); ^{1}H NMR (100 MHz, D_2O) δ 3.05 (3 H, s, NCH_3), 3.47 (4 H, m, 3-CH_2, 4-CH_2), 4.33 (2 H, 2 d, J = 16 Hz, $\Delta\nu$ = 27 Hz, 1-CH_2), 6.77 (1 H, s, 5-CH), 6.82 (1 H, dd, 1 d unresolved, J_m = 2.5, J_o = 8 Hz, 7-CH), 7.10 (1 H, d, J_o = 8 Hz, 8-CH); low-resolution mass spectrum m/e (percent) 163 (M^+, 52), 162 (base peak), 120 (78), 91 (18), 44 (28); ir 3220, 2920, 2680, 2600, 1430, 1200 cm^{-1}. A mixture melting point determination of 2 with the synthetic compound showed no depression. Cochromatography of the isolate with synthetic material showed one spot in solvents A, B, E, F, and G. The isolate and synthetic material exhibited indistinguishable ir spectra.

The free base of compound 3, longimammamine, was converted to the hydrochloride (R_f 0.53, solvent F). Recrystallization from ethanol–ether afforded 3 mg (0.0008% yield) of colorless crystals, mp 224–228°. This compound gave no TLC visualization reaction with fluorescamine, a fluorescent yellow color with dansyl chloride, and a blue-green spot after overspraying with iodoplatinate. A brown spot was observed after spraying 3 with TZB: $[\alpha]^{25}$D −60°; uv max λ (ε) 279 (1700), 216 (4100); ^{1}H NMR (100 MHz, D_2O as solvent and internal standard) δ 3.12 (3 H, s, NCH_3), 3.60 (2 H, broad, 3-CH_2), 4.34 (2 H, 2d, J = 16 Hz, $\Delta\nu$ = 41 Hz, 1-CH_2), 5.07 (1 H, t, J = 3 Hz, 4-CH), 6.92 (1 H, d, J_o = 8 Hz, 7-CH), 7.04 (1 H, d, J_o = 8 Hz, 5-CH), 7.32 (1 H, t, J_o = 8 Hz, 6-CH); low-resolution mass spectrum m/e (percent) 179 (M^+, 16), 136 (21), 135 (18), 107 (10), 77 (11), 44 (base peak); ir 3220, 3170, 3070, 2960, 1460, 1270 cm^{-1}. Cochromatography of the isolate with synthetic material showed one spot in solvent F, as well as identical iodoplatinate and TZB visualization reactions. The ir spectra of the isolated longimammamine hydrochloride and the synthetic material were essentially identical.

Synephrine, compound 4, having R_f 0.18 in solvent F, was crystallized from ethanol and recrystallized to give 25 mg of the colorless free base (mp 183–185°). The ir spectra of synthetic (±)-synephrine (Sigma Chemical Co.) and the isolate were indistinguishable. The isolate exhibited no optical rotation at the sodium D line, and a mixture melting point determination with synthetic (±)-synephrine and the isolate showed no depression (183–186°). Cochromatography of the isolate with the reference in five TLC solvent systems (A, B, E, F, G) showed only one spot, further substantiating the identification.

Extract C, the water-soluble alkaloid fraction, showed two spots (R_f values 0.18 and 0.31, solvent F) with TLC analysis. Upon concentrating this extract to a small volume in ethanol, crystals of synephrine precipitated. Filtration and recrystallization yielded an additional 1.5 g (0.43% yield) of (±)-synephrine. The compound having R_f 0.31 failed to yield crystals, even after preparative TLC.

Resolution and Identification of Nonphenolic Alkaloids. Analytical TLC of this fraction indicated the presence of seven alkaloids that formed yellow fluorophors after being sprayed with dansyl chloride and viewed under uv light, as well as visible chromophores on spraying with TZB. The following R_f values in solvent F were obtained: 0.27, 0.42, 0.47, 0.60, 0.74, 0.79, and 0.85. Preparative TLC (20 plates) was employed to give three crystalline alkaloids, these being the major components of this fraction.

Longimammatine (7) had R_f 0.60 and was isolated as the hydrochloride salt. Recrystallization from ethanol–ether yielded 10 mg (0.0028% yield) of colorless, platelike crystals (mp 244–245.5°, lit.[10] mp 238–239°). Spraying a developed TLC plate with fluorescamine followed by dansyl chloride gave the characteristic fluorophor of a secondary amine. A white spot appeared after overspraying with TZB: uv max λ (ε) 285 (1600), 277 (1700), 226 (7100), 220 (sh, 6500); ^{1}H NMR (100 MHz, D_2O as solvent and internal standard) δ 3.09 (2 H, t, J = 6 Hz, 4-CH_2), 3.50 (2 H, t, J = 6 Hz, 3-CH_2), 3.81 (3 H, s, OCH_3), 4.30 (2 H, s, 1-CH_2), 6.87 (1 H, unresolved d, 5-CH), 6.90 (1 H, d, J_o = 8 Hz, 7-CH), 7.17 (1 H, d, J_o = 8 Hz, 8-CH); low-resolution mass spectrum m/e (percent) 163 (M^+, 53), 162 (base peak), 134 (77), 118 (21), 91 (48), 44 (27); ir 2920, 2830, 2780, 1240, 1215, 1160 cm^{-1}. A mixture melting point determination with the synthetic material showed no depression. This isolate and synthetic reference material showed identical chromatographic mobilities in solvent F, as well as identical TLC color reactions and indistinguishable ir spectra.

Longimammine (8) (R_f 0.42, solvent F) was isolated and converted to the hydrochloride (1.3 mg, 0.00037% yield) with mp 144–146°. Spraying a developed TLC plate with fluorescamine followed by dansyl chloride verified a secondary amine function. A white spot appeared after overspraying with TZB: $[\alpha]^{25}$D −36°; uv max λ (ε) 281 (174), 274 (220), 225 (2100); ^{1}H NMR (100 MHz, D_2O) δ 2.77 (3 H, s, NCH_3), 3.29 (2 H, d, J = 7 Hz, α-CH_2), 3.83 (3 H, s, OCH_3), 5.01 (1 H, t, J = 7 Hz, β-CH), 7.21 (4 H, 2 d, J = 9 Hz, o- and m-H's); low-resolution mass spectrum m/e (percent) 181 (M^+, 3), 137 (15), 44 (base peak). Synthetic (±)-longimammine hydrochloride exhibited mass and ^{1}H NMR spectra indistinguishable from those of the isolate. Cochromatography of the isolate with the reference compound showed one spot in solvents A, B, E, F, and G, as well as identical TLC color reactions.

Normacromerine hydrochloride (9) (R_f 0.27) yielded brown, needle-shaped crystals which were recrystallized from ethanol–ether to give 42 mg (0.012% yield) of the hydrochloride (mp 130–131°, lit.[16a] mp 132–133°). The isolate exhibited $[\alpha]^{25}$D −60.6°; and spectral data (ir, MS, uv, and ^{1}H NMR) obtained with reference (−)-normacromerine hydrochloride[23] and the isolate were essentially identical. A mixture melting point determination showed no depression. Cochromatography of the isolate with the reference in five TLC systems (solvents A, B, E, F, and G) showed one spot, plus identical TLC visualization reactions.

Synthesis of *N*-Methyl-4,6-dihydroxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (6) and Longimammamine Hydrochloride (3). To 20 g (98 mmol) of L-phenylephrine hydrochloride (Sigma Chemical Co.) dissolved in 45 ml of water was added 8 g (99 mmol) of 37% aqueous formaldehyde solution. After 3 days 1.2 g of colorless crystals of 3 was obtained by filtration (TLC showed one spot). The filtrate was reduced to 30 ml with the precipitation of a second crop of crystalline 3, which was recrystallized from water to give 1.7 g. Total yield of 3 was 2.9 g (14 mmol), 14%: mp 235–236.5°; $[\alpha]^{25}$D −40°.

The remaining filtrate was reduced to 20 ml and 70 ml of ethanol was added with the subsequent gradual formation of colorless crystals of 6. This material was recrystallized from methanol–ethanol to give 5.4 g of 6. The filtrate was reduced to 10 ml, and 24 ml of ethanol was added resulting in the formation of an additional 1.5 g of 6. Total yield of 6 was 6.9 g (32 mmol), 33%, mp 193–194°.

Synthesis of Longimmamidine Hydrochloride (1) and Longimammosine Hydrochloride (2). Catalytic hydrogenations of 3 and 6 employing a procedure similar to that described by Bobbitt and Sih[12a] gave 1 and 2, respectively. Thus, 1.9 g (8.8 mmol) of 3 was dissolved in 60 ml of 6 N HCl, and 1.9 g of 5% palladium on carbon was added. Hydrogenation was carried out in a Parr bottle for 44 hr at room temperature and 18 psi. The catalyst was removed by filtration, and the filtrate was condensed to near dryness. Methanol was added and the solution was condensed to near dryness; this procedure was repeated several times. Recrystallization from methanol afforded 0.52 g of 1. TLC of the filtrate (solvent F) showed the presence of some starting material. Preparative TLC (15 plates) was employed to obtain an additional 0.58 g of 1, total yield 1.1 g (5.5 mmol), 63%, mp 247–248.5°, ir indistinguishable from literature ir.[10]

A Parr bottle was charged with 3.1 g (14.4 mmol) of 6, dissolved in 20 ml of 6 N HCl and 3.1 g of 5% palladium on carbon. Hydrogenation was carried out for 7 days at room temperature and 20 psi, after which time hydrogen consumption stopped. TLC of the reaction mixture indicated a 1:1 ratio of starting material to product. The reaction mixture was filtered, a fresh portion (2 g) of 5% palladium on carbon was added, and hydrogenation was continued for 5 days (20 psi), after which time hydrogen consumption ceased. The reaction mixture was filtered, and the filtrate was reduced in volume to near dryness. Methanol was added and the solution was condensed to near dryness; this procedure was repeated several

times. Recrystallization from methanol afforded 0.53 g of colorless crystals of **2**. TLC of the mother liquor indicated some starting material. Preparative TLC (six plates) was employed to obtain an additional 0.69 g of **2**, total yield 1.2 g (6.12 mmol), 43%, mp 234–235.5°.

Synthesis of Longimammine Hydrochloride (8). A Houben–Hoesch condensation of anisole with *N*-methylaminoacetonitrile hydrochloride afforded a 29% yield of 4-methoxy-ω-methylaminoacetophenone hydrochloride, mp 229–230.5°, lit.[24] mp 229–231°. This compound was reduced with sodium borohydride to give optically inactive **8** which was converted to the hydrochloride (mp 116–117°, lit.[20] mp 117–118°).

Synthesis of Longimammatine Hydrochloride (7). The condensation of *m*-methoxybenzaldehyde with nitromethane afforded *m*-methoxy-ω-nitrostyrene (mp 90–91°, lit.[25] mp 91–92°). A lithium aluminum hydride reduction of *m*-methoxy-ω-nitrostyrene afforded *m*-methoxy-β-phenethylamine which was converted to the hydrochloride, mp 129–130.5°. Following slight modification of the procedure described by Helfer,[15] the *m*-methoxy-β-phenethylamine hydrochloride cyclized with formaldehyde to yield **7** (mp 244–245.5°, lit[10] mp 238–239°).

Registry No.—**1**, 34222-77-0; **1** free base, 14788-32-0; **2**, 57196-60-8; **2** free base, 14097-39-3; **3**, 57286-92-7; **3** free base, 57236-57-4; **4**, 582-84-3; **6**, 57196-61-9; **7**, 57196-62-0 **8**, 57286-93-8; **8** HCl, 57236-58-5; **9**, 41136-36-1; L-phenylephrine hydrochloride, 61-76-7; anisole, 100-66-3; *N*-methylaminoacetonitrile, 5616-32-0; *m*-hydroxybenzaldehyde, 100-83-4; nitromethane, 75-52-5.

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Protonated Cyclopropane Intermediates from the Deamination of 3-Methyl-2-aminobutane

Allen G. Meek, Zack Z. Martin, Howard A. Nadworny, and Marc S. Silver*

Department of Chemistry, Amherst College, Amherst, Massachusetts 01002

Received August 20, 1975

The formation of 1,2-dimethylcyclopropanes in the aqueous deamination of 3-methyl-2-aminobutane suggests that the 3-methyl group of the amine plays a role in the reaction. The extent of this role has now been established. Deamination of optically active amine provides *trans*-1,2-dimethylcyclopropane with 57 ± 2% net inversion and 3-methyl-2-butanol with a remarkable 37 ± 3% net *retention* of configuration. Study of the products obtained by deamination of 3-methyl-2-aminobutane-*1,1,1,3-d*$_4$ proves that 37 ± 4% of the 3-methyl-2-butanol formed but essentially none of the 2-methyl-2-butanol has undergone 1,2-methyl rearrangement. A scheme postulating the intervention in the deamination reactions of corner-protonated (methylene carbon) *cis*- and *trans*-1,2-dimethylcyclopropane intermediates adequately rationalizes all the observations. This mechanism cannot be distinguished from one implicating rapidly equilibrating edge-protonated cyclopropane intermediates.

Several carbonium ion reactions apparently generate[1,2] the protonated cyclopropane cation, c-$C_3H_7^+$. For example, postulation that deamination of 1-aminopropane-*1*-^{14}C produces a trace of c-$C_3H_7^+$ provides a simple explanation for the fact that the C_3H_6 fraction obtained contains 10% cyclopropane and that positions 2 and 3 of the 1-propanol formed each contain 2% of the ^{14}C label. Whether c-$C_3H_7^+$ is best represented as edge- or corner-protonated remains undecided.[1,3]

Protonated cyclopropane intermediates seemingly are less important in the deamination of higher alkylamines. The hydrocarbon fraction obtained from deamination of *n*-, *sec*-, or isobutylamine, 1-aminopentane, 2-aminopentane, isopentylamine, or 2-methyl-1-aminobutane contained only 1–5% of the pertinent alkylcyclopropane derivatives.[4,5] Likewise deamination of suitably deuterium-labeled *n*-, *sec*-, or isobutylamine afforded butanols and methylcyclopropane which revealed almost none of the