TABLE III (*Continued*)

Site x[a,b] (solvent)	Code/ ref[c]	Site y[a,b]: –CH₃ (CCl₄)	–OH (DMSO)[d]	(CDCl₃)	 (CDCl₃)	 (CDCl₃)	NH₂ (C_6H_{12})	$N^+(CH_3)_3$ (CH_3CN)	SCH_3 (CCl_4)	Avg $r \times 10^3$
($CDCl_3$)	*m*	[0.81] 0.947(10)	[5.77] 0.920(10)	0.977(12)		0.814(12)	0.763	0.934	0.975(7)	904
($CDCl_3$)	*m*	[1.17] 0.828	[9.38] 0.720(10)	0.733(12)	0.814(12)		0.236	0.765	0.829(7)	704
–CHO (CCl_4)	5	[0.59] 0.919	[3.43] 0.843(8)	0.944(8)	0.936(8)	0.418(8)	0.872	0.959	0.994(5)	861
average *r*		0.929	0.918	0.946	0.916	0.758	0.830	0.929	0.892	

[a] Each system may be represented as XC_6H_4TH, where **H** is the site and **T** the transmitting group. Unless the whole structure is indicated, each system is designated by the site. The average number of substituents was N = 10–11, and the range was N = 6–16. Each entry consists of the correlation coefficient r, sometimes preceded by the slope parameter [s] and followed by (N). [b] The sites listed horizontally supply the δ_{yi} values for eq 3; the vertically listed sites supply δ_{xi}. Since δ_y entries are also included among the δ_x entries, citations are given with the latter set. [c] A number in this column refers to systems coded in ref 2 and 3, where citations are also given. [d] Reference 16. [e] R. Tanaka, this laboratory. [f] This study. [g] Reference 3. [h] Footnote *i*, Table II. [i] B. M. Lynch, B. C. MacDonald, and J. G. K. Webb, *Tetrahedron*, **24**, 3595 (1968). [j] D. A. Tomalia and H. Hart, *Tetrahedron Lett.*, 3389 (1966). [k] Reference 15a. [l] M. A. Weinberger, R. M. Heggie, and H. L. Holmes, *Can. J. Chem.*, **43**, 2585 (1965). [m] Gurudata, J. B. Stothers, and J. D. Talman, *Can. J. Chem.*, **45**, 731 (1967).

relation studies.[15,24] Having recognized that their version of eq 2 was inadequate, Yukawa and Tsuno attempted modifications.[15] Most recently, they have taken certain terms from eq 10, and with appropriate scaling have identified two with polar and resonance effects and utilized another to correct for substituent magnetic anisotropy.[5] The latter takes into account the nature and geometry of the substituent and must be applied individually in any given aryl family. For the several meta-substituted aryl families whose SCS were correlated, the number of substituents was rather small ($N \simeq$ 6–9). And, as was the case with eq 2, it is difficult to see what the polar term means in terms of the chemical structure and there appear to be problems with halogen substituents. It must be conceded, however, that, according to the goodness of fit, the correlations are impressive ($r > 0.99$).[5]

In order to obtain satisfactory correlations of SCS of an aryl family, at least one more term must be added to eq 2. Whatever virtue simplicity has, we have lost it. The question of using extended and/or modified versions of eq 1–3 *vs.* eq 10 for investigating the effect of structure on δ becomes academic and perhaps irrelevant as the two approaches move closer together.

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The Isolation, Structure, Synthesis, and Absolute Configuration of the Cactus Alkaloid Macromerine[1,2]

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(−)-Macromerine has been isolated as the major alkaloid of the cactus *Coryphantha macromeris* and its structure determined to be *N*,*N*-dimethyl-2-hydroxy-2-(3′,4′-dimethoxyphenyl)ethylamine (**3**) from spectral and analytical measurements. Two independent syntheses of racemic macromerine and one of (+)-macromerine (**3a**) were developed. The absolute configuration of (−)-macromerine was shown to be *R* by relating it to (*R*)-(−)-adrenaline (**8**).

Coryphantha macromeris is one of the more alkaloidiferous species found in our recent phytochemical surveys of cacti.[3,4] Chromatography of the crude base fraction on alumina affords the crystalline major alkaloid, macromerine, in 0.16% yield.[5] The molecular weight by mass spectroscopy (225) and the elemental analysis point to a molecular formula of $C_{12}H_{19}NO_3$ for macromerine.

The nmr spectrum in $CDCl_3$ indicates the presence of three aromatic hydrogen atoms, two methoxyl groups, an OH group, and two *N*-methyl groups (downfield shift in acid[6]). The presence of the hydroxyl group is substantiated by the infrared spectrum

(1) Taken from the (a) Masters Thesis and (b) Ph.D. Dissertation of S. D. Brown, Texas Christian University, 1965 and 1969, respectively.

(2) Partially communicated in (a) S. D. Brown and J. E. Hodgkins, 22nd Southwest Regional Meeting of the American Chemical Society, Albuquerque, N. Mex., Dec 1966, Abstracts p 60A; (b) J. E. Hodgkins, S. D. Brown, and J. L. Massingill, *Tetrahedron Lett.*, 1321 (1967).

(3) S. D. Brown, J. L. Massingill, Jr., and J. E. Hodgkins, *Phytochemistry*, **7**, 2031 (1968).

(4) S. D. Brown, J. E. Hodgkins, and M. G. Reinecke, unpublished results.

(5) Subsequent to our initial reports,[2] macromerine also was isolated from *Coryphantha runyonii* by L. E. Below, A. Y. Leung, J. L. McLaughlin, and A. G. Paul, *J. Pharm. Sci.*, **57**, 515 (1968).

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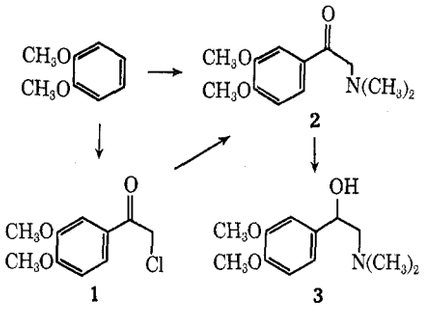
(3125 cm^{-1}) and the *N*-methyl groups by the occurrence of a base peak in the mass spectrum at *m/e* 58 [$CH_2N(CH_3)_2^+$].[7]

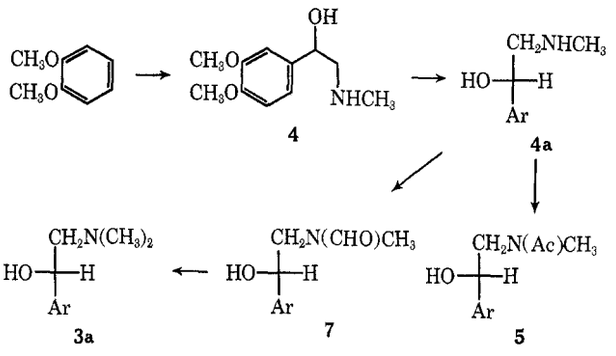
The remainder of the nmr spectrum consists of two coupled sets of double doublets centered at δ 4.60 (1 H) and 2.35 (2 H, partially overlapped by the NMe peak in $DCCl_3$ but separated in D_2O). Since the high field set of peaks moved downfield in acid they were assigned to the CH_2N group. The magnetic nonequivalence of these hydrogens suggests that the remaining hydrogen atom, to which these are coupled, must be on an asymmetric carbon atom and therefore leads to the partial structure $(MeO)_2C_6H_3CHOHCH_2N(CH_3)_2$ for macromerine.

By analogy with the known cactus alkaloids[8] the aromatic ring of macromerine is probably substituted as shown in **3**. The presence of ortho-methoxy groups is substantiated by the peaks at *m/e* 95 and 123 in the mass spectrum,[9] and the 1,2,4 pattern is consistent with the infrared spectrum in the 800–900-cm^{-1} region.[10]

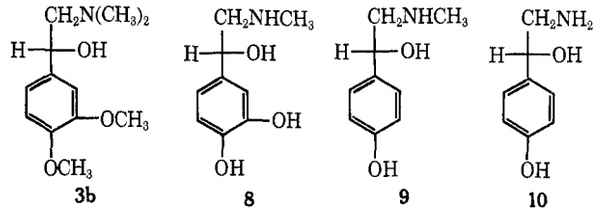
The final proof of structure, however, rests on the two syntheses[11] of (±)-macromerine. Both proceed by reduction of the amino ketone **2**, which is prepared from veratrole by either a Hoesch condensation[12] or by a Friedel–Crafts acylation[13] followed by reaction of the resulting chloro ketone **1** with dimethylamine. The former route is the more convenient and proceeds in higher overall yield (23%).



The structural relationship of macromerine (**3**) to adrenaline (**8**) (the former is the O^3,O^4,N-trimethyl derivative of the latter) prompted an investigation of the configurational relationship of these compounds. The racemic dimethyl ether of adrenaline (**4**) was prepared from veratrole by the same method[12] used to synthesize macromerine. Resolution of **4** *via* the *d*-α-bromocamphor-π-sulfonate salt led to the (+) enantiomer **4a**, which was shown to have the *S* configuration by its conversion to the known[14] (*S*)-(+)-acetamide (**5**). Formylation and reduction[15] of **4a** gave (+)-macromerine (**3a**), the enantiomer of natural (−)-macromerine (**3b**). Since **5** is the enantiomer of the acetamide **6** obtained[14] from adrenaline (**8**), both natural macromerine (**3b**) and natural adrenaline (**8**) must have the *R* configuration. This same relationship also is true[14] for naturally occurring synephrine (**9**)[16] and octopamine (**10**).[16–18]



Ar = 3,4-dimethoxphenyl



Because of the structural similarity of macromerine to adrenaline, mescaline, and other psychotomimetic agents,[19] a study of its physiological and psychopharmacological properties is underway.[1a,2b,20]

Experimental Section

All melting points were taken on a Koefler micro hot stage and are corrected. Microanalyses were performed by Scandinavian Microanalytical Laboratory, Box 25, Herlev, Denmark, or M-H-W Laboratories, P. O. Box 326, Garden City, Mich. 48135. Infrared spectra were taken of KBr discs on a Perkin-Elmer Model 237 instrument. Nmr spectra were recorded on a Varian A-60 spectrometer of $DCCl_3$ solutions with tetramethylsilane as an internal standard, unless otherwise indicated. The uv spectra were measured on a Cary 15 spectrophotometer. Mass spectra were obtained on a Finnegan Model 1015SL instrument at 70 eV. Optical rotations were taken on a Rudolph Model 76 polarimeter.

Extraction of Alkaloids.—The cactus *Coryphantha macromeris* was collected in Big Bend National Park, Brewster County, Texas.[21] The dried (50–55°, *ca.* 10% of the wet weight), powdered plant (500 g) was extracted with 95% EtOH and 0.5% HOAc for 6 days. The extracts were concentrated *in vacuo*, and water and concentrated HCl were added to give an alcohol-free solution containing *ca.* 5% HCl. The aqueous solution was washed with ether, made basic with Na_2CO_3, and extracted with ether in a continuous liquid–liquid extractor. The ether extracts were reextracted with 5% HCl, and the aqueous solutions were made basic (Na_2CO_3) and then extracted once again with ether. The purified ether extracts were dried (Na_2SO_4) and concentrated, leaving 2 g of a dark, viscous oil. Another 2 g of

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(21) We wish to thank Professor Lyman Benson, Pomona College, Claremont, Calif., for aid in classification and the United States Department of the Interior, National Park Service, for permission to harvest the plant in Big Bend National Park, Tex.

crude alkaloids was obtained by continuously extracting the first ether exhausted basic aqueous solution with CH_2Cl_2 for 24 hr.

The crude alkaloid mixture (6.37 g) from several extractions was chromatographed on 264 g of activity grade IV neutral Woelm Al_2O_3 with 400 ml of 1:1 ether–petroleum ether (bp 30–60°) to yield 2.72 g of crystalline macromerine, mp 63–65°. Rechromatography, treatment with charcoal, and recrystallization from ether yielded 2.50 g of analytically pure (−)-macromerine (**3b**): mp 66–67.5°; $[\alpha]^{25}D$ −42.6° (*c* 0.020, EtOH), −147.0° (*c* 0.0390, $CHCl_3$); nmr δ 2.25 [s, 7 H, $HCHN(CH_3)_2$], 2.35 [d, 1, J = 5 Hz, $HCHN(CH_3)_2$], 3.88 (s, 3, OCH_3), 3.93 (s, 3, OCH_3), 3.85 (s, 1, shifts with concentration changes and disappears in D_2O, OH), 4.52 and 4.66 [double d, 1, J = 5 Hz, $CHCH_2N(CH_3)_2$], 6.85 (broad s, 2, ArH), 6.95 (broad d, 1, ArH); ir 805, 875, 3125 cm^{-1} (broad); uv max (95% EtOH) 231 mμ (log ε 4.18); mass spectrum *m/e* (rel intensity) 225 (0.02) 208 (0.03), 192 (0.02), 180 (0.02), 167 (0.12), 166 (0.12), 165 (0.15), 164 (0.04), 151 (0.10), 139 (0.57), 123 (0.70), 108 (0.50), 95 (1.0), 81 (0.90), 77 (2.4), 58 (100) (lit.[5] *m/e* 225, 208, 207, 192, 180, 167, 166, 165, 164, 151).

Anal. Calcd for $C_{12}H_{19}NO_3$ (**3b**): C, 63.96; H, 8.52; N, 6.22. Found: C, 63.98; H, 8.56; N, 6.13.

3,4-Dimethoxy-ω-dimethylaminoacetopheneone (2). A.[12]—A stirred mixture of 110 ml of dry nitrobenzene, 68 g (0.51 mol) of $AlCl_3$, 27.2 g (0.23 mol) of dimethylaminoacetonitrole hydrochloride, and 31.2 g (0.23 mol) of veratrole was protected from moisture and held at 20° while dry HCl gas was bubbled through the mixture for 8 hr. The resulting viscous solution was poured into 225 ml of H_2O, boiled for 10 min, and cooled, the organic layer was decanted, and the aqueous solution was cooled to 0°. The crystals which formed were recrystallized from ethanol–2-butanone four times, yielding 22.5 g (39%) of **2** hydrochloride after drying over P_2O_5 *in vacuo*, mp 193–196° dec, ir 1685 cm^{-1} (C=O). Without the vacuum drying, the salt forms a hydrate, melting at 100°, which resolidifies and melts at 193–196°.

Anal. Calcd for $C_{12}H_{18}NClO_3$ (**2a** HCl): C, 55.49; H, 6.94; N, 5.40. Found: C, 55.39; H, 7.04; N, 5.23.

B.—3,4-Dimethoxy-ω-chloroacetopheneone (**1**) (34.6 g), prepared from veratrole by the method of Tutin,[13] was dissolved in 100 ml of absolute EtOH and added to a solution of 72.6 g of dimethylamine in 110 ml of absolute EtOH in a 500-ml boiling flask equipped with a reflux condenser and a $CaCl_2$ drying tube. The solution was stirred for 2 hr at room temperature and 2 hr at 60°, after which it was cooled at room temperature for 24 hr. The dimethylamine hydrochloride was precipitated with anhydrous ether, filtered, and washed with ether, and the combined filtrates were concentrated *in vacuo*. The residual oil was taken up in ether, dried (Na_2SO_4), and the ether removed by distillation *in vacuo*, leaving 26 g of **2** as a thick yellow oil which solidified overnight, mp 48–56°, hydrochloride mp 193–196° dec.

(±)-Macromerine (3).—A solution of 10 g (0.039 mol) of **2** hydrochloride in 50 ml of water containing 1.85 g (0.05 mol) of $NaBH_4$ was stirred for 2 hr and extracted with ether, and the ether was dried (Na_2SO_4) and removed *in vacuo*. The residual oil was recrystallized from dry ether–*n*-hexane (1:1) three times to give 5.1 g (59%) of **3**, mp 47.5–48.5°. The ir (CS_2), nmr, and uv spectra of **3** were identical with those of natural (−)-macromerine. A picrate was prepared, mp 147–148° (lit.[11] 157°).

Anal. Calcd for $C_{18}H_{22}N_4O_{10}$ (**3** picrate): C, 47.55; H, 4.89; N, 12.34. Found: C, 47.49; H, 5.02; N, 12.09.

***N*-Methyl-2-hydroxy-2-(3′,4′-dimethoxyphenyl)ethylamine (Adrenaline Dimethyl Ether) (4).**—To a solution of 20 g (0.08 mol) of *N*-methyl-2-keto-2-(3′,4′-dimethoxyphenyl)-ethylamine[12] in 60 ml of H_2O was slowly added 6.4 g (0.17 mol) of $NaBH_4$. The mixture was stirred for 2 hr and extracted with CH_2Cl_2, and the extracts were dried over Na_2SO_4. After removal of the solvent *in vacuo*, 16 g (82%) of **4** was obtained which after two recrystallizations from EtOAc melted at 107–108.5° (lit.[12] 103–105°).

Resolution of 4.—(−)-α-Bromocamphor-π-sulfonic acid ammonium salt (5.94 g, 0.018 mol) and 3.82 g (0.018 mol) of **4** were mixed in 100 ml of MeOH. The solvent was successively removed and added until the odor of ammonia was not longer present. The resulting glass was dissolved in EtOH, treated with charcoal, and recrystallized from EtOH–EtOAc to a constant melting point of 150.5–151.0° and rotation $[\alpha]^{26}D$ of +84.7° (*c* 0.034, EtOH).

Anal. Calcd for $C_{21}H_{32}BrNO_7S$ (**4a** bromocamphorsulfonate): C, 48.26; H, 6.13; N, 2.68; Br, 15.33; S, 6.13. Found: C, 48.28; H, 6.04; N, 2.70; Br, 16.15; S, 6.04.

A solution of 5.36 g (0.0099 mol) of the above salt in 100 ml of 1.5 *M* NH_4OH was extracted with ten 20-ml portions of CH_2Cl_2. The CH_2Cl_2 extracts were washed with 20 ml of 1.5 *M* NH_4OH, H_2O, and two 30-ml portions of saturated salt solution and dried over Na_2SO_4. The solvent was removed at reduced pressure, leaving 2.06 g (0.0098 mol) of oil **4a**, $[\alpha]^{28}D$ +23.48° (*c* 0.0921, EtOH), hydrochloride mp 130–131.

Anal. Calcd for $C_{11}H_{18}NO_3Cl$ (**4a** HCl): C, 53.33; H, 7.27; N, 5.66. Found: C, 53.30; H, 7.43; N, 5.61.

4a Acetamide (5).—Following the procedure of Pratesi, *et al.*,[14] 0.155 g of the resolved amine **4a** was converted to 0.106 g of the acetamide **5** after one recrystallization from benzene: mp 127–128°; $[\alpha]^{25}D$ +70.0° (*c* 0.00383, $CHCl_3$) [lit.[14] mp 123–124°, $[\alpha]^{18}D$ +77.4 (1.13% w/v in $CHCl_3$)]; nmr δ 2.00 (s, 3, $NCOCH_3$), 2.90 (s, 3, NCH_3), 3.39 (d, 1, J = 5 Hz, HCHN), 3.56 (d, 1, J = 5 Hz, HCHN), 3.87 (s, 6, 2 OCH_3), 4.87 and 4.96 (double d, 1, J = 5 Hz, $HCCH_2N$), 6.69 (broad s, 2, ArH), 6.80 (broad s, 1, ArH).

Anal. Calcd for $C_{13}H_{19}NO_4$ (**5**): C, 61.63; H, 7.58; N, 5.53. Found: C, 61.52; H, 7.77; N, 5.39.

4a Foramamide (7).—To a solution of 1.90 g (9 mmol) of the resolved amine **4a** in 50 ml of freshly distilled, dried (Na_2SO_4) $CHCl_3$ at 0° was added 1.33 g (9 mmol) of Cl_3CCHO freshly distilled from sulfuric acid. The solution was stirred for 5 min at 0° and 5.5 hr at room temperature, after which the $CHCl_3$ was removed at reduced pressure. The residual oil was dried by repeated solution in dry benzene followed by evaporation at reduced pressure. Eventually concentration to *ca.* 20 ml gave 1.37 g (65%) of **7**, which after recrystallization from benzene had mp 88–90°; $[\alpha]^{25}D$ +44.1° (*c* 0.0229, EtOH); nmr δ 2.88 (s, 3, NCH_3), 3.35 (d, 1, J = 5 Hz, HCHN), 3.52 (d, 1, J = 5 Hz, HCHN), 3.87 (s, 6, 2 OCH_3), 4.68 and 4.82 (double d, 1, J = 5 Hz, $HCCH_2N$), 6.90 (m, 3, ArH), 7.96 (s, 1, NCHO).

Anal. Calcd for $C_{12}H_{17}NO_4$ (**7**): C, 60.23; H, 7.18; N, 5.85. Found: C, 59.96; H, 7.28; N, 5.73.

(+)-Macromerine (3a).—A perforated aluminum cup containing 0.189 g (7.9 mmol) of the formamide **7** was fitted into a 24/40 to 14/20 adapter attached to a 100-ml 14/20 flask charged with 2.98 g of $LiAlH_4$ in 50 ml of dry ether. A 24/40 condenser equipped with a $CaCl_2$ drying tube was fitted on the adapter and the ether was heated under reflux until all the formamide was in solution (32 hr) and then for 12 hr longer. Excess $LiAlH_4$ was destroyed at 0° by the dropwise addition of the calculated amount of water with vigorous stirring. The mixture was filtered, the granular precipitate was washed with $CHCl_3$ (100 ml), the ether and $CHCl_3$ wash were combined and dried (Na_2SO_4), and the solvent was removed at reduced pressure to give 0.096 g of crude **3a** (mp 50–60°). Chromatography on 3 g of Woelm activity IV Al_2O_3 with 5:1 ether–*n*-hexane yielded in the second 50 ml fraction 0.014 g of pure **3a** (glc), mp 59–62°, $[\alpha]^{26}D$ +34.2° (*c* 0.0354, absolute EtOH). The ir and nmr spectra of synthetic (+)-macromerine (**3a**) and natural (−)-macromerine (**3b**) are identical.

Registry No.—**2**, 33061-24-4; **2** (HCl), 33061-25-5; **(±)-3**, 33122-27-9; **3a**, 33066-27-2; **3b**, 33066-28-3; **4a** (bromocamphorsulfonate), 33066-29-4; **4a** (HCl), 33066-30-7; **5**, 33066-31-8; **7**, 33066-32-9.

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