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SYNTHESIS OF (+)-MEARSINE

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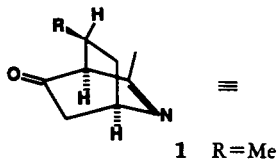
ABSTRACT.—A stereoselective synthesis of (+)-mearsine [**2**], the enantiomer of the natural alkaloid, has been achieved. Its success provides confirmation of the structure and stereochemistry assigned to the natural base by earlier workers.

(−)-Mearsine is a minor alkaloid of the North Queensland plant *Peripentadenia mearsii* (C.T. White) L.S. Smith (Elaeocarpaceae), native to the rain forests of that region. It was isolated and characterized in 1984 by Robertson *et al.* (1) who, on the basis of spectral measurements and X-ray diffraction analysis, advanced structure **1** to represent the absolute configuration of the compound. The structure is unusual in that a charge transfer occurs between the azomethine and carbonyl groups, reflected in the uv absorption spectrum (1).

We describe here a stereoselective synthesis of (+)-mearsine [**2**], the enantiomer of



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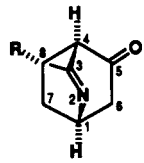

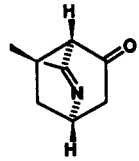

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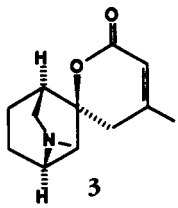

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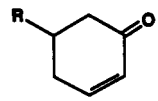

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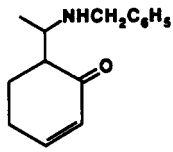

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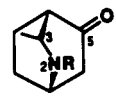

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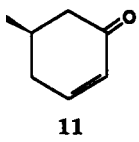
9 R=H
10 R=Cl



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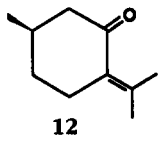

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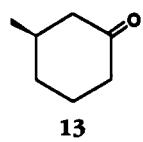

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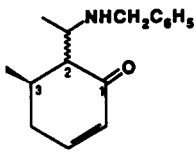

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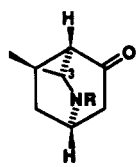

15 R=Bz
16 R=H
17 R=Cl

the natural base, which corroborates the stereostructure advanced for the alkaloid (1).

Our synthetic strategy was prompted by recognition of a structural resemblance between mearsine and dioscorine [**3**], an alkaloid synthesized some years ago by one of us (2,3). It was reasoned that a similar synthetic route might be applied to mearsine [**1**], with substitution of acetaldehyde for formaldehyde in the first step (Mannich reaction), to accommodate the methyl group at position 3 in **1**, and use of 5-methyl-2-cyclohexenone [**4**] to provide the other methyl group at position 8. Also, in this step, benzylamine would replace methylamine, to lead to an *N*-benzyloxoisoquinuclidine, capable of manipulation to afford the azomethine group in mearsine.

Because cyclohex-2-enone is commercially available whereas the ketone **4** had to be synthesized, we decided first to test the feasibility of the proposed sequence by applying it to the former ketone, to lead, hopefully, to normearsine [**5**]. Thus a Mannich reaction between **6**, acetaldehyde, and benzylamine yielded the anticipated mixture of normal Mannich base **7** and its intramolecular cycloaddition product **8**, separable by the Hinsberg procedure. The latter compound, 2-benzyl-3-methyl-5-oxoisoquinuclidine [**8**], was debenzylated to 3-methyl-5-oxoisoquinuclidine [**9**], presumably a mixture of diastereomers. The azomethine 2,3 double bond was then established by a Ruschig reaction sequence (4) (chlorination to **10**, then dehydrochlorination), affording normearsine [**5**] in excellent yield.

The successful sequence was then applied to (+)-mearsine, the absolute stereochemistry shown in structure **2** which required (−)-5-methyl-2-cyclohexenone [**11**] as starting point. This ketone was secured from poley oil, the essential oil of *Mentha pulegium* L., which contained 85% (+)-pulegone [**12**]. The latter ketone, obtained by careful fractionation, was cleaved hydrolytically to (+)-3-methylcyclohexanone [**13**] (5), which was subjected sequentially to bromination, ketalization, dehydrobromination, and hydrolysis to provide (−)-5-methyl-2-cyclohexenone [**11**] (5–9). Ketone **11** was then subjected to the same Mannich reaction to afford a 1:1 mixture of bases **14** and **15**, easily separable by chromatography. Inspection of a model of **14** suggested that the intramolecular Michael addition product would be **15**, in which for steric reasons the C-*N* bridge appears on the α face of **14**, the side opposite to the β-3-methyl group. Product **15** is presumably a mixture of two diastereomers; it was hydrogenolyzed catalytically to **16**, homogeneous on gc and tlc evidence.

Compound **16** was chlorinated to **17**, then dehydrochlorinated to yield (+)-mearsine [**2**] in 87% yield after purification. Gc and tlc analyses showed the product was >90% pure. It was purified via its crystalline picrate, yielding a crystalline base, mp 41.5–42° [lit. (1) mp 43–44° for natural (−)-mearsine]. We were unable to secure an authentic sample of the natural alkaloid for direct comparison, but the data in Table 1 leave little doubt that natural and synthetic bases are identical in all respects except optical rotation.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mp's are uncorrected. Ir spectra were measured on a Perkin-Elmer 1310 instrument as liquid films. ^{1}H- and ^{13}C-nmr spectra were recorded on JEOL FX-900 and Perkin-Elmer-Hitachi R-24 instruments in $CDCl_3$ with TMS as internal standard. Mass spectra were determined on a Hewlett-Packard 5985A- GC/MS instrument. Gc analyses were performed on a Perkin-Elmer Sigma 3b instrument. Uv spectra were obtained using a Carey 2000 spectrometer with 95% EtOH as solvent. Ir measurements were on liquid films. Elemental analyses are by Atlantic Microlab, Atlanta, Georgia. Cc was performed using Woelm Si gel (63–200), and tlc separations were effected with Merck Kieselgel 60G.

2-BENZYL-3-METHYL-5-OXOISOQUINUCLIDINE [**8**].—Benzylamine hydrochloride (7.15 g, 0.05 mol), 2-cyclohexenone (4.81 g, 0.05 mol, freshly distilled), metaldehyde (26.4 g, 0.15 mol), MeOH (10 ml), and concentrated HCl (4 drops) were refluxed and stirred magnetically for 12 h. Solvent was then re-

TABLE 1. Comparison of the Properties of (−)-Mearsine [**1**] and Synthetic (+)-Mearsine [**2**].

	(−)-Mearsine [**1**][a]	Synthetic (+)-Mearsine [**2**]
Free base, mp	43–44°	41.5–42°
Picrate, mp	212–213° (dec.)	209–210° (dec.)
Uv absorption λ max (EtOH)	234 nm (log ε 3.67) 275 nm (log ε 2.78)	232 nm (log ε 3.67) 272 nm (log ε 2.79)
Ir absorption ν max (film)	1730, 1660, 1630 cm^{-1}	1729, 1661, 1630 cm^{-1}
^1H nmr spectrum δ, ppm (TMS = 0)	4.51 b, 3.25 d, 2.11 m, 1.97 m, 1.25 dd, 1.03 d	4.50 bs, 3.27 d, 2.10 m, 1.94 m, 1.30 m, 1.04 d
^{13}C nmr spectrum δ, ppm (TMS = 0), proton-noise decoupled	208, 173.9, 61.5, 55.8, 39.6, 32.6, 28.9, 24.4, 21.1	208, 174, 61.1, 56.0, 39.8, 32.4, 28.6, 24.5, 21.5
Mass spectrum, *m/z*	152, 151, 136, 94, 69, 68, 55	152, 151, 136, 94, 69, 68, 55
$[\alpha]_D$ (CH_2Cl_2)	−34.5° (*c* = 0.495) (17°)	+32.1° (*c* = 0.5) (20°)

[a]Data in this column are from Robertson *et al.* (1).

moved in vacuo. H_2O (15 ml) and concentrated HCl (few drops) were added and the whole subjected to continuous Et_2O extraction for 12 h. The aqueous layer was basified with excess K_2CO_3 and extracted thoroughly with Et_2O. The combined, dried (Na_2SO_4) extracts were concentrated, finally in vacuo, leaving a crude mixture (12.5 g) of amines, which was distilled fractionally. The main fraction distilled at 110–120° (0.025 torr) (6.8 g) as a colorless oil, which, on gc evidence, was a 1:1 mixture of **7** and **8**. The mixture of bases (6.8 g, 0.03 mol) in pyridine (5 ml) was cooled in ice and agitated during the gradual addition of benzenesulfonyl chloride (5.73 g, 0.033 mol) in pyridine (6 ml). After being warmed to ambient temperature, the mixture was heated on the steam bath for several minutes, then cooled and stirred at room temperature for 3 h. HCl (3 N) was added until the system was acidic; then neutral material was removed by Et_2O extraction. The aqueous layer was basified with excess K_2CO_3 at 0°, and the liberated base **8** taken up in Et_2O. The dried extracts were concentrated, finally in vacuo at 80°. The residue was distilled: bp 110–113° (0.01 torr) (3.27 g); ν max 1720, 1500, 1170, 725, 690 cm^{-1}; δ 1.06 (3H, d, $J = 6.4$), 1.95 (1H, m), 2.20 (4H, m), 2.8 (3H, m), 3.69 (2H, s), 7.30 (5H); eims *m/z* $[M + 1]^+$ 230, $[M]^+$ 229, 215, 214, 186, 173, 172, 158, 132, 92, 91 (base peak), 65 (found C 77.6, H 8.4, $C_{15}H_{19}NO$ requires C 78.6, H 8.3%). The picrate separated from MeOH in bright yellow needles: mp 183–183.5° (dec.) (found C 55.05, H 4.85, $C_{21}H_{22}N_4O_8$ requires C 55.0, H 4.8%).

3-METHYL-5-OXOISOQUINUCLIDINE [**9**].—The foregoing ketobase (500 mg, 2.18 mmole) in MeOH (15 ml) was stirred in H_2 at room temperature in the presence of palladized carbon (100 mg of 5%) until gas absorption ceased (58.0 ml, 1 mol). The suspension was filtered through Celite, and the filtrate was concentrated in vacuo. The residual 3-methyl-5-oxoisoquinuclidine [**9**] distilled at 90–93° (0.01 torr) (282) mg, 93%): ν max 3320, 1720, 1450, 1320, 1100, cm^{-1}; δ 1.11 (3H, d, $J = 6.4$), 1.93 (4H, m), 2.20 (1H, s), 2.37 (3H, bs), 3.35 (2H, m); ^{13}C nmr δ 23.5, 25.1, 27.0, 48.3, 48.8, 50.5, 52.9, 215.6 (found C 69.0, H 9.2, $C_8H_{13}NO$ requires C 69.1, H 9.35%).

2-CHLORO-3-METHYL-5-OXOISOQUINUCLIDINE [**10**].—3-Methyl-5-oxoisoquinuclidine (102 mg, 0.73 mmol) in pentane (40 ml) was stirred for 1 h at room temperature with *N*-chlorosuccinimide (137 mg, 1.0 mmol). The suspension was filtered and the solvent evaporated under reduced pressure, leaving a light yellow oil (123 mg, 97%). This *N*-chloro-compound was unstable and was used immediately without purification.

NORMEARSINE [**5**].—The foregoing *N*-chloroketone (123 mg, 0.71 mmol) in hexane (9.3 ml) was stirred for 2 h at room temperature with freshly prepared potassium *t*-butoxide (134 mg, 1.2 mmol). The suspension was filtered and the solvent removed in vacuo. The yellow, oily residue of normearsine distilled at 80–82° (0.005 torr) (87.8 mg, 90%): ν max 1729, 1662, 1631, 1450, 1325, 1102 cm^{-1}; δ 2.12 (4H, m), 2.15 (3H, s), 2.27 (2H, bs), 3.20 (1H, m), 4.5 (1H, bs); ^{13}C nmr δ 25.1, 30.2, 32.4, 41.7, 56.9, 62.5, 175, 209; cims *m/z* $[M]^+$ 137 (base peak), 122, 96, 95, 94, 81, 80, 70, 68, 67, 57, 56, 55, 54; uv λ max 230 nm (log ε 3.66), 270 nm (log ε 2.78). The picrate crystallized from MeOH in yellow needles: mp 204–207° (dec.) (found C 45.9, H 3.8, $C_{14}H_{14}N_4O_8$ requires C 45.9, H 3.85%).

(−)-5-METHYL-2-CYCLOHEXENONE [**11**].—This ketone was synthesized from commercial (+)-pulegone by sequential hydrolysis, bromination, ketalization, dehydrobromination, and hydrolysis (5–9).

2-BENZYL-3,8-DIMETHYL-5-OXOISOQUINUCLIDINE [**15**].— This enone (5.50 g, 0.05 mol), metaldehyde (26.4 g, 0.15 mol), benzylamine hydrochloride (7.15 g, 0.05 mol), MeOH (15 ml), and concentrated HCl (5 drops) were stirred and refluxed for 16 h. The solvent was removed in vacuo, and H_2O (40 ml) and further concentrated HCl (3 drops) were added. Neutral material was removed by continuous Et_2O extraction, and the aqueous layer was basified with excess K_2CO_3 and extracted several times with Et_2O. The combined, dried (Na_2SO_4) extracts were concentrated in vacuo and the dark, oily residue was distilled fractionally, the major fraction, bp 115–122° (0.025 torr) (6.1 g), being collected; it was a 1:1 mixture of **14** and **15** on gc evidence. This mixture (500 mg) in pentane-Et_2O (3:1) was chromatographed on Si gel (20 g), the desired tertiary ketobase **15** being eluted with the same solvent combination (224 mg): ν max 1722, 1498, 1168, 720 cm^{-1}; δ 1.02 (3H, d, $J = 9$ Hz), 1.06 (3H, d, $J = 6.4$ Hz), 1.89 (3H, m), 1.93 (1H, m), 2.61 (3H, m), 3.70 (2H, s), 7.31 (5H, s); eims *m/z* $[M]^+$ 243, 229, 228, 200, 187, 186, 172, 146, 92, 91 (base peak). The picrate separated from MeOH in yellow needles: mp 176–177° (dec.) (found C 56.0, H 5.15, $C_{22}H_{24}N_4O_8$ requires C 55.9, H 5.1%).

3,8-DIMETHYL-5-OXOISOQUINUCLIDINE.—This benzylisoquinuclidine (500 mg, 2.06 mmol) was hydrogenolyzed catalytically in MeOH exactly as described for the nor-compound (see above). The product distilled at 95–98° (0.005 torr) (283 mg, 90%), and was 99.4% pure by gc analysis: ν max 1719, 1450, 1100 cm^{-1}; δ 1.07 (3H, d, $J = 9.0$ Hz), 1.11 (3H, d, $J = 6.4$ Hz), 1.98 (3H, m), 2.31 (1H, s), 2.39 (3H, bs), 3.38 (2H, m); ^{13}C nmr δ 20.6, 23.2, 26.4, 29.2, 48.9, 50.1, 51.5, 54.4, 216. The picrate crystallized from MeOH in bright yellow prisms: mp 211–213° (dec.) (found C 47.2, H 4.8, $C_{15}H_{18}N_4O_8$ requires C 47.1, H 4.75%).

2-CHLORO-3,8-DIMETHYL-5-OXOISOQUINUCLIDINE [**17**].—This *N*-chloroamine was prepared as outlined in the nor-series (see above) from the foregoing amine (72 mg), 0.47 mmol) and *N*-chlorosuccinimide (88 mg, 0.66 mmol) in pentane (32 ml). A light yellow, unstable oil was obtained (86 mg, 98%) which was used immediately.

(+)-MEARSINE [**2**].—This chloroamine (86 mg, 0.46 mmol) in dry hexane (6.0 ml) was stirred with potassium *t*-butoxide (87.3 mg, 0.8 mmol) for 2 h at room temperature. The suspension was filtered and the solvent removed in vacuo. The residual (+)-mearsine [**2**] distilled at 85–87° (0.005 torr) (61 mg, 87%); it was homogeneous on gc evidence. It was purified by conversion in the usual way to the picrate, which separated from MeOH in yellow prisms, mp 209–210° (dec.) [lit. (1) mp 212–213° (dec.) for (−)-mearsine picrate]. This picrate (1.90 g) was suspended in Et_2O (50 ml) and shaken repeatedly with 20-ml portions of concentrated NH_4OH until the aqueous layer was no longer yellow. The Et_2O layer was dried and evaporated in vacuo, leaving (+)-mearsine (705 mg, 93%), which solidified on keeping at 0°. A sample was sublimed in vacuo, mp 41.5–42° (found C 71.4, H 8.4, $C_9H_{13}NO$ requires C 71.5, H 8.6%). For comparison with natural (−)-mearsine see Table 1: ν max 1729, 1661, 1630, 1449, 1322 cm^{-1}; δ 1.04 (3H, d, $J = 9$ Hz), 1.30 (1H, m), 1.94 (2H, m), 3.27 (1H, d, $J = 3$ Hz), 4.50 (1H, bs); ^{13}C nmr δ 21.5, 24.5, 28.6, 32.4, 39.8, 56.0, 61.1, 174, 208; eims *m/z* $[M]^+$ 151 (base peak) 136, 94, 69, 68, 55; uv λ max 232 nm (log ϵ 3.67), 272 nm (log ϵ 2.78); $[\alpha]_D$ +32.1° ($c = 0.5$, CH_2Cl_2).

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