quinolizone and pyridine protons), and 3.9 (3 H, singlet methyl protons). The compound obtained in this way was sufficiently pure for use in the next step of the synthesis. A sample was purified for analysis by sublimation at 150° (0.05 mm) as bright yellow, needle-shaped crystals, mp 171–173°.

Anal. Calcd for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; mol wt, 280. Found: C, 68.54; H, 4.31; mol wt, 280 (mass spectrum).

***r*-(1*R*,3*R*,10*S*)-1-Carbomethoxy-3-(2-pyridyl)-4-quinolizidinone[7] (9c).**—A stirred (magnetic) solution of 1-carbomethoxy-3-(2-pyridyl)-4-quinolizone (8) (25.7 g, 0.0918 mol) in absolute methanol (400 ml), containing a suspension of 10% palladium on charcoal catalyst (9.2 g), was hydrogenated at ambient temperature and pressure. After a volume of hydrogen corresponding to 4 equiv was absorbed (3 days), the solid catalyst was separated from the reaction mixture by filtration of the latter through a Celite bed. Ordinarily the volume of the filtrate was reduced (evaporation) to 150 ml, and the resulting solution was used in the isomer equilibration step (below).

In one instance, however, the filtrate was evaporated to dryness, and the residue was dissolved in the minimum volume of methanol and placed onto a column of alumina (150 g, Woelm, nonalkaline, Activity Grade III) that was previously packed (flow method, *n*-hexane). Development of the column gave one major, diffuse, slightly yellow band, which was eluted with ether. Removal of the ether gave a mass of yellow-colored semisolid material (*ca.* 85% of the original weight) that was examined by means of its nmr spectrum. In addition to the changes expected from hydrogenation of the quinolizone ring in **8**, the presence of only two different signals owing to the methoxyl protons (δ 3.63 and 3.67) was consistent with a mixture of stereoisomeric forms of **9**.

The mixture was converted (equilibrated) to essentially one isomer by dissolving sodium (2.1 g, 0.091 g-atom) in absolute methanol (*ca.* 30 ml), adding the resulting solution to the concentrated methanol filtrate (above), and heating the resulting solution during 2 hr under reflux. After the mixture was cooled and neutralized with acetic acid, the whole was evaporated to leave an oily semisolid. This was chromatographed on alumina (Woelm, nonalkaline, Activity Grade III) as described above. Evaporation of the ether eluant gave *r*-(1*R*,3*R*,10*S*)-1-carbomethoxy-3-(2-pyridyl)-4-quinolizidinone (**9c**): yield 23 g (86%); pale yellow needles; mp 133–136°; ir ($CHCl_3$) 3000, 1600, 1575 (pyridyl), 1635 (lactam carbonyl), 2950, 2865, 1740, 1260, and 1170 cm^{-1} (carbomethoxy); nmr ($CDCl_3$) δ 8.45, 7.55, 7.12 (multiplets, 1 H, 1 H, 2 H, pyridyl protons), 3.65 (singlet, 3 H, methoxyl protons and quinolizidinone protons), 4.78 (broad doublet, 1 H), 3.7 (partially obscured multiplet, 1 H), 2.5 (broad envelope, 4 H), and 1.7 (broad envelope, 7 H).

Recrystallization of the compound from an acetone and hexane mixture gave colorless needles, mp 143–145°.

Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.64; H, 6.99; mol wt, 288. Found: C, 66.50; H, 7.03; mol wt, 288 (mass spectrum).

***r*-(1*R*,3*S*,10*S*)-1-Hydroxymethyl-3-(2-pyridyl)quinolizidine (4).[7]**—A solution of **9c** (2.88 g, 0.0100 mol) in tetrahydrofuran (THF) (50 ml) was added dropwise to a stirred suspension of lithium aluminum hydride (1.5 g, 0.039 mol) in THF (50 ml). After the addition was complete, the reaction mixture was boiled gently (reflux) for 2 hr before it was cooled and hydrolyzed by careful successive additions of water (1.5 ml), 15% aqueous sodium hydroxide solution (1.5 ml), and finally water (4.5 ml). The coagulated alumina was separated by filtration and washed with THF. The combined washings and filtrate was evaporated to give the amino alcohol **4** as a very viscous yellow oil[8]: yield 2.2 g (89%); ir ($CHCl_3$) 3630, 3300 (free and bonded hydroxyl), 2863, 2920, 2778 (*trans*-quinolizidine), 1600, 1575, 1480, and 1440 cm^{-1} (pyridyl); nmr ($CDCl_3$) δ 8.42, 7.50, 7.08 (doublet of triplets, 1 H, apparent pentet, 1 H, triplet of doublets, 2 H, all pyridyl protons), 3.75, 2.90, 1.70 (broad doublet, 5 H, broad triplet, 3 H, broad envelope, 11 H, quinolizidine and hydroxymethyl protons).

Conversion of *r*-(1*R*,3*S*,10*S*)-1-Hydroxymethyl-3-(2-pyridyl)-quinolizidine (4) to (±)-Anagyrine (3).—The following account is a modification of the original procedure of van Tamelen and Baran.[6]

The amino alcohol **4** (2.2 g, 0.0089 mol), as obtained from the previous step, was dissolved in 48% aqueous hydrobromic acid (60 ml) and heated under reflux for 22 hr. All solvent was evaporated from the acidic reaction mixture under reduced pressure (*ca.* 35 mm). The residue was dissolved in water (20 ml) before the whole was cooled in an ice bath and transferred to a separatory funnel (benzene washes). The cold solution of hydrobromide salt was made strongly basic by the addition of cold, 3 *N* sodium hydroxide. The liberated bromo amine was quickly extracted into cold benzene (50 ml). After the combined benzene extracts were dried (anhydrous sodium sulfate), they were boiled under gentle reflux for 2 hr. Recrystallization (acetone) of the collected crystalline material deposited from the benzene solution gave the crude tetracyclic quaternary salt **6**, yield 492 mg (18%), mp 209–214° (lit.[6] mp 209–215°).

To a portion of this material (**6**) (356 mg, 1.15 mmol) dissolved in water (2 ml) was added an aqueous solution (4 ml) of sodium hydroxide (600 mg, 15 mmol) and potassium ferricyanide (800 mg, 2.43 mmol), and the whole was heated on a steam bath during 24 hr after an additional portion of water (2 ml) was used to clarify the cloudy reaction mixture. The cooled solution was exhaustively extracted with benzene (15 × 5 ml), and the combined extracts were dried (anhydrous sodium sulfate), filtered, and evaporated to a residue which was introduced into a modified Späth bulb and molecularly distilled [150° (0.05 mm), air bath] to give (±)-anagyrine (**3**): yield 129 mg (46.0%); pale yellow glass. This material was identical with authentic (−)-anagyrine generated from its hydrobromide salt,[16] as shown by chromatographic behavior [tlc, R_f 0.29 (acetone)] and by superimposability of infrared spectra.

Registry No.—**3**, 34389-11-2; **4**, 34389-12-3; **8** (R = CH_3), 34407-56-2; **9c**, 34407-57-3.

(16) L. Light and Co. Ltd., Colnbrook, England.

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

S. D. BROWN, J. E. HODGKINS, J. L. MASSINGILL, JR., AND M. G. REINECKE*

Department of Chemistry, Texas Christian University, Fort Worth, Texas 76129

Received September 1, 1971

The predominant feature of the desert landscape of southern Arizona and western Sonora, Mexico, is the giant sahuaro cactus, *Carnegiea gigantea.*[3] The presence of alkaloids in this cactus was discovered over 40 years ago with the isolation[4] and the determination[5] of structure of carnegine (**1**).

As part of our survey of cactus alkaloids[6,7] the basic fraction of *C. gigantea* was reexamined by gas chromatography[8] and found to contain at least two major and two minor alkaloids. The most abundant alkaloid (70% of the basic fraction) was an optically inactive oil which was characterized as carnegine (**1**) by comparison of its properties and those of its derivatives with a synthetic sample.[5] The other major alkaloid (25–30% of the basic fraction in the whole plant or about 50% in the growing tip) was obtained as an optically active crystalline solid whose properties differed from those of the

(1) Taken from the Texas Christian University Ph.D. Dissertations of (a) J. L. Massingill, 1968 [*Diss. Abstr.*, **29**, 2814B (1969)] and (b) S. D. Brown, 1969 [*ibid.*, **30**, 3547B (1970)].

(2) Preliminary communication: S. D. Brown and M. G. Reinecke, 24th Southwest Regional Meeting of the American Chemical Society, Austin, Texas, Dec 1968, Abstracts, p 95.

(3) N. L. Britton and J. N. Rose, "The Cactaceae," Vol. II, The Carnegie Institute of Washington, Washington, D. C., 1920, p 164.

(4) G. Heyl, *Arch. Pharm.*, **266**, 668 (1928).

(5) E. Späth, *Chem. Ber.*, **62**, 1021 (1929).

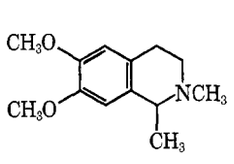
(6) S. D. Brown, J. L. Massingill, Jr., and J. E. Hodgkins, *Phytochemistry*, **7**, 2031 (1968).

(7) S. D. Brown, J. E. Hodgkins, and M. G. Reinecke, unpublished work.

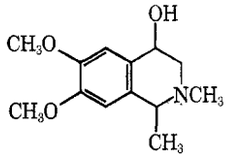
(8) J. L. Massingill, Jr., and J. E. Hodgkins, *Anal. Chem.*, **37**, 952 (1965).

known cactus alkaloids.[9-11] This new alkaloid was named gigantine.[12] The minor alkaloids probably are phenethylamines[13,14] and salsolidine (**2**).[14] The report[14] that the latter is a major alkaloid of *C. gigantea* could not be verified with any of the plant samples at our disposal.

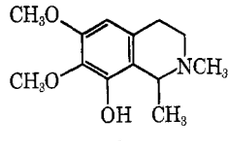
Analytical and spectral data[12] suggested that gigantine is a hydroxycarnegine. The originally proposed[12] structure **3** was rendered untenable by the observation that gigantine was not identical with either the cis or trans isomers of synthetic **3**.[15] The reexamination initiated by this discovery led to the conclusion[6] that gigantine must be a positional isomer of the phenolic isoquinoline alkaloid pellotine (**4**)[16] which, in contrast to gigantine, is always isolated as the racemate. This last fact is probably due to the remarkably facile racemization of optically active pellotine[17] compared to gigantine, which is stable to racemization under much more severe treatment (see Experimental Section).



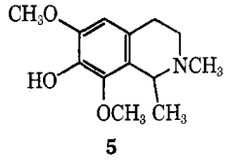
1



3



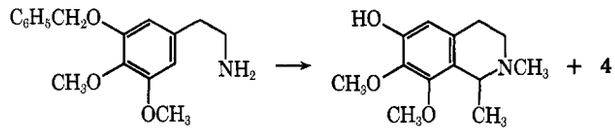
4



5

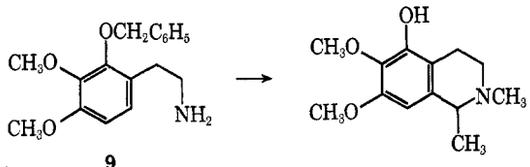
By analogy to the known cactus alkaloids[9-11] the oxygen substituents of gigantine should appear at positions 6, 7, and 8. This restriction generates two possible structures (**5** and **6**) in addition to pellotine (**4**). The former[18] was eliminated because its nmr spectrum[19] differed from that of gigantine. The physical and spectral properties of **6**, synthesized from the acetamide of the known[20] phenethylamine **7** by a Bischler–Napieralski cyclization followed by methylation and reduction, also differed from gigantine. Of the nine remaining possible isomers all but **8** were eliminated by the observation that the Gibbs' test[21] for phenols with a free para position is positive for gigantine.

This assignment was confirmed by the total synthesis of **8** from the known[22] phenethylamine **9** by the identical method used above for **6**. Since our initial



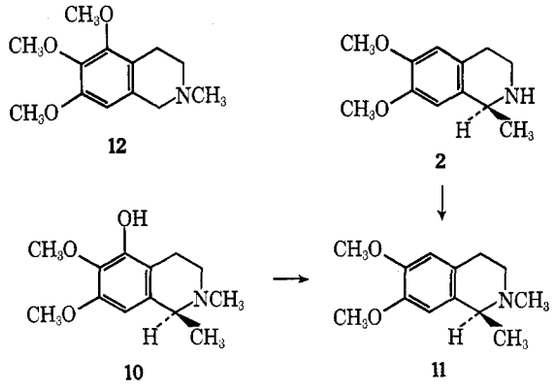
7 **6**

disclosures of this work[1,2] two preliminary communications over similar total syntheses of (±)-gigantine[23,24] and its (±)-methyl ether[25] have appeared. The melting point reported for (±)-gigantine in one of these papers[24] is the same as that of natural gigantine and differs from ours by 30°. The reason for this discrepancy is unknown.



9 **8**

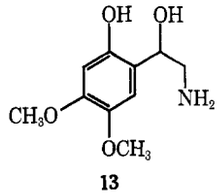
Gigantine was shown to have the *S* configuration (**10**) by converting it, *via* reductive cleavage of its diethylphosphate ester,[26] to (*S*)-carnegine (**11**) which has been related to (*S*)-salsolidine (**2**).[27]



12 **2**

10 **11**

Gigantine possesses the rare[28] 5,6,7-trioxygenated pattern previously found in only one other simple isoquinoline alkaloid, tehaunine (**12**) from the cactus *Pachycereus tehauntepecanus*.[29] The presence of the 5-hydroxy group suggests a possible relationship between gigantine and the hypothetical[30] endogenous psychotogen of schizophrenia (**13**). Preliminary tests[12] indicate that gigantine does have hallucinogenic properties, and more detailed studies are in progress.[31]



13

(9) L. Reti, *Fortsch. Chem. Org. Naturst.*, **6**, 242 (1950).
(10) L. Reti, *Alkaloids*, **4**, 23 (1954).
(11) H. G. Boit, "Ergebnesse der Alkaloid Chemie bis 1960," Akademie-Verlag, West Berlin, 1961, pp 13, 210.
(12) J. E. Hodgkins, S. D. Brown, and J. L. Massingill, *Tetrahedron Lett.*, 1321 (1967).
(13) C. Steelink, M. Yeung, and R. Caldwell, *Phytochemistry*, **6**, 1435 (1967).
(14) J. G. Bruhn, U. Svensson, and S. Agurell, *Acta Chem. Scand.*, **24**, 3775 (1970).
(15) G. Grethe, M. Uskovic, T. Williams, and A. Brossi, *Helv. Chim. Acta*, **50**, 2397 (1967); J. M. Bobbitt, private communication, 1967.
(16) A. Heffter, *Chem. Ber.*, **27**, 2975 (1894).
(17) E. Späth and F. Kesztler, *ibid.*, **69**, 755 (1936).
(18) A. Brossi and R. Borer, *Monatsh. Chem.*, **96**, 1409 (1965).
(19) Kindly supplied by Drs. A. Brossi and W. Leimgruber.
(20) A. Brossi, F. Schenker, R. Schmidt, R. Banziger, and W. Leimgruber, *Helv. Chim. Acta*, **49**, 403 (1966).
(21) F. E. King, T. J. King, and L. C. Manning, *J. Chem. Soc.*, 563 (1957).
(22) T. Kametani, S. Kano, Y. Watanabe, and T. Kikuchi, *Yakugaku Zasshi*, **87**, 406 (1967).
(23) G. J. Kapadia, G. S. Rao, M. B. E. Fayez, B. K. Chowdhury, and M. L. Sethi, *Chem. Ind. (London)*, 1593 (1970).
(24) A. M. Choudhury, *ibid.*, 578 (1971).
(25) G. J. Kapadia, M. B. E. Fayez, M. L. Sethi, and G. S. Rao, *Chem. Commun.*, 856 (1970).
(26) S. W. Pelletier and D. M. Locke, *J. Org. Chem.*, **23**, 131 (1958).
(27) A. R. Battersby and T. P. Edwards, *J. Chem. Soc.*, 1214 (1960).
(28) T. Kametani, "The Chemistry of the Isoquinoline Alkaloids," Elsevier, Amsterdam, 1969.
(29) F. L. Weisenborn, private communication cited in ref 25.
(30) A. T. Shulgin, T. Sargent, and C. Naranjo, *Nature (London)*, **221**, 537 (1969).
(31) J. C. Hitt, S. Winokur, and M. G. Reinecke, research in progress.

Experimental Section

Melting points were taken on a Koefler hot stage apparatus and are corrected. Nmr spectra were recorded on a Varian A-60A spectrometer in $CDCl_3$ solution with tetramethylsilane as an internal reference. The uv spectrum was measured on a Cary 15 spectrophotometer and the infared spectra were taken on a Perkin-Elmer Model 237 spectrophotometer. Optical rotations were measured with a Rudolph Model 76 polarimeter. The mass spectrum was recorded on a modified[32] CEC-21-103A instrument at 70 eV. Analyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark, and M-H-W Laboratories, Garden City, Mich.

Isolation of Carnegine (1) and Gigantine (10).—A section of a branch from a sample of *Carnegia gigantea*[3] collected[6] in Maricopa County, Ariz., was diced (3–4 cm^3), dried (50°), and powdered in a Waring blender, and 783 g of it was extracted for 2 days from EtOH containing 0.5% HOAc in a modified Soxhlet extractor. The extracts were condensed at reduced pressure and diluted with 5% HCl, the remainder of the EtOH was removed, and the resulting alcohol-free solution was made up to a volume of *ca.* 600 ml with 5% HCl. The filtered solution was extracted with ether until fresh extracts were colorless, basified with K_2CO_3, and continuously extracted with $CHCl_3$ in a liquid–liquid extractor. The $CHCl_3$ extract was dried (Na_2SO_4) and concentrated at reduced pressure to give 10.2 g (1.3%) of crude bases which were cleanly separated into two fractions by chromatography on 300 g of Alcoa F-20 alumina. Elution with 1:1 hexane–benzene yielded 6.8 g of carnegine (1) as an optically inactive oil whose infrared and nmr spectra [δ 3.88 (s, 6, OCH_3), 2.90 (s, 3, NCH_3), 4.49 (q, J = 7 Hz, 1, $CHCH_3$), 1.28 (d, J = 7 Hz, 3, $CHCH_3$), 6.68 (s, 2, ArH), 3.5–3.8 (m, 4, CH_2)] were identical with those of a synthetic sample:[5] **1 HCl**, mp 209–211° (lit.[5] mp 210–211°); **1 picrate**, mp 211–213° (lit.[5] mp 212–213°); **1 MeI**, mp 209–211° (lit.[5] mp 210–211°); mass spectrum *m/e* (rel intensity) 221 (3), 207 (12), 206 (100), 190 (10), 178 (4), 162 (5), 148 (4), 103 (6), 91 (6), 77 (6), 58 (17).

Elution of the column with 1:1 benzene–ether yielded 2.4 g of crystalline gigantine (10), which after recrystallization from ether melted at 151–152°; $[\alpha]^{25}D$ +27° (*c* 1.99, $CHCl_3$); ir ($CHCl_3$) 3530 cm^{-1} (OH); nmr δ 1.37 (d, J = 6 Hz, 3, $CHCH_3$), 2.45 (s, 3, NCH_3), 2.90 (m, 4, CH_2CH_2N), 3.53 (q, J = 6 Hz, 1, $CHCH_3$), 3.82, (s, 3, OCH_3), 3.84 (s, 3, OCH_3), 6.18 (s, 1, ArH), 6.60 (broad s, 1, OH, shifts with concentration changes); mass spectrum *m/e* (rel intensity) 237 (4), 222 (100), 206 (22), 194 (25), 179 (25), 161 (10), 111 (5), 91 (12), 77 (15), 58 (60); uv max (95% EtOH) 205 mμ (log ϵ 4.8).

Anal. Calcd for $C_{13}H_{19}NO_3$ (10): C, 65.83; H, 8.02; N, 5.91. Found: C, 65.68; H, 8.12; N, 6.00.

A hydrochloride, mp 221.5–222.5° from absolute EtOH, was prepared.

Anal. Calcd for $C_{13}H_{20}NO_3Cl$ (**10 HCl**): C, 57.03; H, 7.37; N, 5.12. Found: C, 56.91; H, 7.46; N, 4.89.

Gigantine gave a positive $FeCl_3$ test in methanol but not in $CHCl_3$.[33] It was recovered in 50–90% optical purity after treatment with (i) 2% KOH in EtOH, 5 hr, reflux; (ii) 2 *M* aqueous KOH, 48 hr, reflux; (iii) 2% KO-*t*-Bu in DMSO, 24 hr, 70°.

1,3-Dimethyl-6-hydroxy-7,8-dimethoxyisoquinoline (6).—A stirred solution of 6 g (0.02 mol) of 3-benzyloxy-4,5-dimethoxyphenylethylamine (7)[20] in 5% HCl and 10 ml of Ac_2O was basified with solid $NaHCO_3$ and then allowed to react for 30 min. The precipitated crude amide, mp 93–94°, was dried by dissolving it in 150 ml of dry benzene and removing half the solvent by distillation. To the resulting solution was added 4.7 ml of $POCl_3$ and the mixture was heated to 80° for 2 hr on a water bath. Removal of the volatiles on a rotary evaporator left a residue which was taken up in 10% H_2SO_4. The acid solution was washed with benzene, cooled, and basified with NaOH, and the basic solution was extracted with $CHCl_3$. The $CHCl_3$ extracts were washed (H_2O), dried (Na_2SO_4), and evaporated to leave 4.3 g (70%) of a golden oil.

A 3.1-g portion of this oil was dissolved in 100 ml of MeOH and heated to reflux with 4 g of MeI for 1.5 hr. After concentrating the solution to 50 ml, 2 g of $NaBH_4$ was added, the mixture was stirred for 10 min, the volume was concentrated to 20 ml, 150 ml of 1 *M* NaOH was added, and the resulting mixture was extracted with $CHCl_3$. Evaporation of the washed (H_2O) and dried (Na_2SO_4) $CHCl_3$ extracts yielded 2.83 g of a mixture of the benzyloxy derivatives of 4 and 6 which could not be satisfactorily separated by chromatography on Al_2O_3 and was therefore dissolved in 100 ml of HOAc and hydrogenated at 30 psi in a Parr apparatus in the presence of 2 g of 5% Pd/C. Removal of the catalyst and evaporation of the solvent left 1.4 g of a mixture of 4 and 6 which was separated by chromatography on Alcoa F-20 Al_2O_3. Benzene eluted pellotine (4), mp 111–112° (lit.[17] mp 111–112°), whose infared spectrum was identical with that of an authentic sample.[19] Benzene–Et_2O (3:2) eluted 6: mp 131.5–132.5°; nmr δ 1.25 (d, J = 6.2 Hz, 3, C-Me), 2.41 (s, 3, N-Me), 2.5–3.0 (m, 4, CH_2), 3.78 (s, 3, OMe), 3.80 (s, 3, OMe), 3.84 (q, J = 6.2 Hz, 1, CH), 6.24 (s, 1, ArH), 6.62 (broad s, 1, OH).

Anal. Calcd for $C_{13}H_{19}NO_3$ (6): C, 65.80; H, 8.07; N, 5.90. Found: C, 65.92; H, 8.29; N, 5.90.

1,2-Dimethyl-6,7-dimethoxy-5-hydroxytetrahydroisoquinoline [(±)-Gigantine] (8).—A mixture of 6 g of β-(2-benzyloxy-3,4-dimethoxyphenyl)ethylamine (9)[22] and 50 ml of Ac_2O was allowed to react overnight at room temperature, at which time the excess Ac_2O was removed on a rotary evaporator. A benzene solution of the residue was extracted with three portions of 5% HCl and one portion of saturated NaCl and dried over Na_2SO_4, and the solvent was removed at reduced pressure to give 9 acetamide as a vpc-pure oil: nmr (CCl_4) δ 1.75 (s, 3, Ac), 2.70–3.25 (m, 4, CH_2CH_2), 3.68 (s, 3, OMe), 3.73 (s, 3, OMe), 4.95 (s, 2, OCH_2), 6.43 (d, J = 9 Hz, 1, ArH), 6.70 (d, J = 9 Hz, 1, ArH), 7.20 (m, 5, C_6H_5 and NH); ir 1650 cm^{-1}.

A solution of the above amide in 50 ml of dry benzene and 3 ml of freshly distilled $POCl_3$ was heated to reflux for 3 hr and then allowed to stand at room temperature overnight. The reaction mixture was extracted with two 100-ml portions of 1 *N* NaOH, 100 ml of H_2O, and 100 ml of saturated NaCl and dried over $CaSO_4$, and the solvent was evaporated at reduced pressure to give **5-benzyloxy-6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline** as a vpc-pure oil: nmr (CCl_4) δ 2.23 (s, 3, 1-Me), 2.48–3.40 (m, 4, CH_2CH_2), 3.77 (s, 3, OMe), 3.81 (s, 3, OMe), 4.93 (s, 2, OCH_2), 6.70 (s, 1, ArH), 7.25 (m, 6, C_6H_5 and NH); ir 1625 cm^{-1}.

Reaction with methyl iodide gave 4.4 g (46% from 9) of **5-benzyloxy-6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline methiodide** as a yellow solid, which after two recrystallizations from 2-butanone had melting point 164–166°.

Anal. Calcd for $C_{20}H_{24}NO_3I$: C, 52.98; H, 5.30; N, 3.09. Found: C, 53.09; H, 5.16; N, 2.98.

To a solution of 3.8 g of the above methiodide in 50 ml of MeOH was added, in portions, 2.5 g of $NaBH_4$. After the exothermic reaction subsided, the solvent was removed at reduced pressure and the residue was dissolved in 100 ml of ether. The ether solution was extracted with three 50-ml portions of 3% NaOH, one of H_2O, and one of saturated NaCl, dried over Na_2SO_4, and evaporated at reduced pressure to give 2.3 g (85%) of oily **5-benzyloxy-6,7-dimethoxy-1,2-dimethyltetrahydroisoquinoline**: nmr (CCl_4) δ 1.30 (d, J = 6 Hz, 3, 1-Me), 2.32 (s, 3, N-Me), 2.60 (m, 4, CH_2CH_2), 3.42 (q, J = 6 Hz, 1, $CHCH_3$), 3.75 (s, 3, OMe), 3.80 (s, 3, OMe), 4.96 (s, 2, OCH_2), 6.30 (s, 1, ArH), 7.24 (m, 5, C_6H_5). A picrate, mp 168–169° dec, was prepared.

Anal. Calcd for $C_{26}H_{28}N_4O_{10}$: C, 56.12; H, 5.04; N, 10.07. Found: C, 56.31; H, 4.94; N, 9.86.

A mixture of 1.08 g of the above isoquinoline in 20 ml of HOAc was hydrogenated in the presence of 0.5 g of 5% Pd/C for 2 hr at 30 psi and room temperature. After filtration and removal of the solvent at reduced pressure, the resultant residue was dissolved in 50 ml of benzene and extracted with three 50-ml portions of 1 *N* NaOH. The combined basic extracts were adjusted to pH 9–10 with concentrated HCl and Na_2CO_3 and then extracted with three 50-ml portions of $CHCl_3$. Drying (saturated NaCl and $CaSO_4$) and evaporation of the $CHCl_3$ at reduced pressure gave 0.4 g (53%) of crude (±)-gigantine (8). Chromatography on Woelm activity IV Al_2O_3 followed by recrystallization from ether gave material of mp 121–123° whose nmr ($DCCl_3$) and ir ($DCCl_3$ or CS_2) spectra were identical with those of natural (+)-gigantine.

Conversion of Gigantine (10) to (*S*)-Carnegine (11).[26]—A solution of 1.03 g (0.004 mol) of gigantine and 0.64 g (0.005 mol) of $HOP(OEt)_2$[34] in 14 ml of CCl_4 was treated with 0.47 g of freshly

(32) M. J. O'Neal and T. P. Wier, *Anal. Chem.*, **23**, 830 (1950).
(33) S. Soloway and S. H. Wilen, *ibid.*, **24**, 979 (1952).
(34) H. McCombie, B. C. Saunders, and G. J. Stacy, *J. Chem. Soc.*, 380 (1945).

distilled triethylamine and stirred at room temperature for 48 hr. The reaction mixture was diluted with 30 ml of $CHCl_3$ and extracted with 3% NaOH (3 × 20 ml) to remove 0.475 g of unreacted gigantine. The $CHCl_3$ layer was washed with saturated NaCl solution and dried over $CaSO_4$, the solvent was evaporated, and residual water was removed by azeotropic distillation with 50 ml of dry benzene.

The crude phosphate ester (1.353 g, 84%) was dissolved in 5 ml of dry, peroxide-free THF in a flask equipped with a Dry Ice condenser and a $CaCl_2$ drying tube. About 10 ml of dry NH_3 was passed through a NaOH drying tower and condensed into the reaction flask. The reaction mixture was cooled in an acetone–Dry Ice bath while 0.172 g (0.008 g-atom) of sodium metal was added in small pieces. The solution was allowed to warm up until the ammonia began to reflux in order to prevent the phosphate ester from crystallizing. When the blue color of the dissolved sodium vanished (30 min), 5 ml of absolute ethanol was added and the ammonia was allowed to evaporate. The residue was dissolved in $CHCl_3$ (100 ml), and the solution was extracted with water (3 × 50 ml), dried by shaking with a saturated salt solution (2 × 50 ml), and filtered through $CaSO_4$. Distillation of the solvent at reduced pressure left (*S*)-carnegine [(−)-*N*-methylsalsolidine] (**11**) as an oil which was converted to 0.475 g (43% from **10**) of an hydrochloride, whose infrared spectrum (KBr) and that of the hydrochloride of natural, racemic carnegine (**1**) were identical, as were the nmr spectra ($DCCl_3$) of the free bases (**11** and **1**); a picrate, mp 229–232° (lit.[27] mp 233–234°), was also prepared. A distilled (0.03 mm) sample of the free base **11** regenerated from this picrate by passage through an Al_2O_3 column with $CHCl_3$–CH_3OH had the following rotations: $[M]^{25}D$ −110° (*c* 1.78, benzene), −51.5° (*c* 1.70 absolute EtOH), and +16.5° (*c* 1.22, 1 *N* HCl) [lit.[27] $[M]^{22}D$ −115 °(*c* ~4.5, benzene), −55° (*c* 4.45, absolute EtOH), and +17° (*c* ~4.5, 1 *N* HCl)].

Registry No.—**1**, 490-53-9; **6**, 34407-54-0; **9** acetamide, 30666-18-3; **10**, 34408-15-6; **10** HCl, 34408-16-7; 5-benzyloxy-6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline, 30666-19-4, 34402-63-6 (methiodide); 5-benzyloxy-6,7-dimethoxy-1,2-dimethyltetrahydroisoquinoline, 34389-05-4, 34402-64-7 (picrate).

Acknowledgment.—This research was generously supported by grants from the Texas Christian University Research Foundation and the Robert A. Welch Foundation. We would also like to thank Mr. Chongsuh Pyun and Mr. Robert Daubert for experimental assistance, Mr. Ernst Ellis for the preparation of (±)-carnegine, Dr. J. R. Zimmerman and the Mobil Oil Co. of Dallas for the mass spectra, and Mr. W. H. Earle, Director of Desert Botanical Gardens, Tempe, Ariz., for classifying *C. gigantea*.

Convenient Synthesis of Frontalin—1,5-Dimethyl-6,8-dioxabicyclo[3.2.1]octane

T. D. J. D'Silva* and D. W. Peck

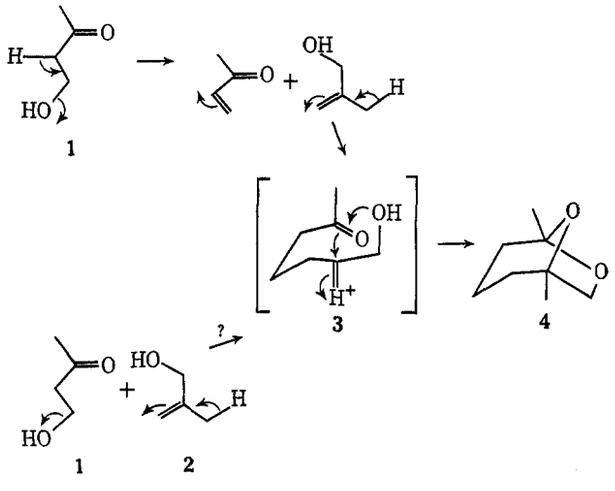
Research and Development Department, Union Carbide Corporation, Chemicals and Plastics, South Charleston, West Virgina 25303

Received December 27, 1971

Frontalin is an aggregating pheromone of the southern pine beetle and other related bark beetles.[1] Kinzer, *et al.*,[2] reported the synthesis of the attractant without experimental details, and in unspecified yield,[3] by heating methyl vinyl ketone (MVK) and methallyl alcohol. We wish to report a simple, one-step synthesis of frontalin by heating a mixture of formaldehyde (as formalin, paraformaldehyde, or trioxane), excess of acetone, and methallyl alcohol, *without any catalyst*, in a stainless steel autoclave or sealed glass tube at 250–275° for 1 hr. Up to 35–40% of frontalin (based on methallyl alcohol consumed) has been isolated. The yield of frontalin was markedly increased (see Experimental Section) with toluene as solvent, albeit with a loss in efficiency due to loss of methallyl alcohol.

Although the yields have not been optimized, this process offers great advantage over the use of MVK or other synthetic routes for the large-scale production of frontalin.

Heating methallyl alcohol with 4-hydroxy-2-butanone, the first reaction product between formaldehyde and acetone, also yields frontalin. From glc analysis of the samples taken at shorter reaction times, MVK and its dimer have been detected (in one instance MVK was also isolated), but they disappear with time. It is, therefore, apparent that the reaction leading to the formation of frontalin proceeds *via* the intermediary of MVK formed *in situ*. This could then react with methallyl alcohol in Diels–Alder fashion[2] or by an "ene-type reaction" as shown below. A direct reaction between methallyl alcohol and 4-hydroxy-2-butanone, although less likely, cannot be ruled out.



Some of the physical properties of frontalin are recorded in the Experimental Section.

Experimental Section

Synthesis of Frontalin Using Acetone and Paraformaldehyde without Solvent.—A suspension of 480.0 g (16.0 mol) of paraformaldehyde, 1152.0 g (16.0 mol) of methallyl alcohol, and 6720.0 g (96.0 mol) of acetone was heated in a 5-gallon autoclave for 1 hr at 250°. Distillation yielded 6070.0 g of acetone, 31.0 g of methyl vinyl ketone, 770.0 g of methallyl alcohol, 267.0 g of frontalin (~98% pure), bp 60–62° (30 mm), 450.0 g of high-boiling fraction, bp 142–162° (0.8–0.9 mm), and 322.0 g of residue. Pure frontalin had bp 155° (760 mm), 91° (100 mm), $n^{20}D$ 1.4386, sp gr (20°) 0.9889. Its nmr spectrum was identical with that of the material obtained by Kinzer's method. The yield of frontalin based on reacted methallyl alcohol was 35.4%.

(1) J. P. Vité and G. P. Pitman, *J. Econ. Entomol.*, **63**, 1132 (1970), and references cited therein.

(2) G. W. Kinzer, A. F. Feintiman, Jr., T. F. Page, Jr., R. L. Foltz, J. P. Vité, and G. P. Pitman, *Nature (London)*, **221**, 477 (1969).

(3) B. P. Mundy, R. D. Otzenberger, and A. R. DeBernardis, *J. Org. Chem.*, **36**, 2390 (1971), recently reported the synthesis *via* a Diels–Alder reaction of MVK and methyl methacrylate, followed by reduction to the alcohol and cyclization, in overall yields of less than 10%.