not only from cleavage of **8** but also from further reactions of the *N*-lithioimine that would result from initial loss of a methyl group. The precursor of **9** should not be prone to disappearance by conversion to intractable materials. In fact, the yield of **9** matches that of **2**, a product of further reaction in which *all* alkyl groups of **9** have been lost.

Even making allowance for the statistical factor favoring loss of methyl, it is likely that the primary alkyl group is cleaved in preference to a methyl group in the initial cleavage of **8**. Other results[3] suggest, though less conclusively, that phenyl and 2-phenylethynyl (PhC≡C) groups also are cleaved particularly rapidly. The results are in accord with carbanionic but not radical character developing on the group being cleaved in the rate-determining step of the cleavage. A similar conclusion was drawn from a study of the loss of alkyl groups (generally primary > secondary > tertiary) from alkoxides.[4]

Experimental Section

^{1}H NMR spectra were taken at 60 MHz with Me_4Si as an internal reference. Absorptions are reported with the following notations: s, singlet; m, complex multiplet; c, complex overlapping absorptions. Analytical and preparative GC separations were performed by using a thermal-conductivity instrument with helium as the carrier gas and the following columns constructed out of aluminum tubing: A, XE-60 (15%) on Gas Chrom Q (80–100 mesh), 0.25 in. × 6 ft; B, SF-96 (10%) on Chromosorb W (45–60 mesh), 0.25 in. × 6 ft. The *n*-butyllithium was a commerical (Ventron Corp.) hexane solution (~2.4 M); hydrolysis of this solution produced some octane which was noted in all GC analyses of reaction products. The amines were commercial samples (Aldrich Chemical Co.). Hexane was stored over Na.

Reaction Procedure. The amine, dissolved in hexane (ca. 2 mL/mmol), was added slowly (ca. 15 min) to the *n*-butyllithium solution which was maintained under a positive pressure of nitrogen, cooled in an ice bath, and magnetically stirred. The reaction mixture then was heated at reflux temperature and stirred for the specified period of time. Ethanol or methanol (15 mL) was added, followed by addition of water (15 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (2 × 10 mL), and the combined organic layers were dried ($MgSO_4$). Most of the solvent was removed either in vacuo or by distillation using a small Vigreux column; this procedure would have removed any products with volatilities comparable to or greater than hexane.

Product mixtures generally were subjected to GC analysis. By use of glass U-shaped tubes inserted into the exit port of the gas chromatograph and cooled in liquid nitrogen, small samples of each significant component were collected for spectral analysis. The structures of products were determined from their NMR and IR spectra. Spectra are reported here only for compounds for which authentic samples are not readily available.

When GC analysis was used to determine yields, a known weight of a linear alkane generally was added to the crude product. Yields were determined by assuming that the detector responded equally to equal weights of different compounds.

Reaction of 1,1-Dimethyl-2-phenyl-1-ethanamine (6). GC analysis (column B, 135 °C) of the reaction that had a 1:4 ratio of amine to *n*-butyllithium gave three peaks. Peak 1 (relative retention time 1.0) was due to **7**, peak 2 (1.1) to **2**, and peak 3 (2.0) to **6**. Yields were determined by using undecane (1.6) as the internal standard.

A reaction using a 1:1 ratio of reactants gave a crude product (85%) having NMR and IR spectra virtually identical with those of **6** and exhibiting principally the GC peak due to **6**.

Reaction of 1,1-Dimethyl-1-hexadecanamine (8). GC analysis (column A) gave five peaks. Peak 1 (relative retention time 1.0) was due to **2**, peak 2 (1.2) to **9**, and peak 3 (23) to **8**. Peak 4 (29) was due to **10**: IR (CCl_4) 1720 cm^{-1} (C=O); ^{1}H NMR (CCl_4) τ 7.61 (m, 2, CH_2C=O), 7.91 (s, 3, CH_3C=O), 8.71 (c, 26, $CH_3(CH_2)_{13}$), 9.11 (m, 3, CH_3CH_2). Peak 5 (77) was due to **11**: IR (CCl_4) 1720 cm^{-1} (C=O); ^{1}H NMR (CCl_4) τ 7.70 (c, 4, CH_2COCH_2), 8.72 (c, 30, other CH_2's), 9.10 (m, 6, CH_3). Compounds **10** and **11** solidified in the collection tubes. Yields were determined using heptadecane as the internal standard.

Reaction of 2,2,4-Trimethyl-2-pentanamine (12). GC analysis (column B, 120 °C) gave four peaks. Peak 1 (relative retention time 1.0) was due to **13**: IR (CCl_4) 1710 cm^{-1} (C=O); ^{1}H NMR (CCl_4) τ 7.73 (s, 2, CH_2), 7.95 (s, 3, CH_3C=O), 8.98 (s, 9, $(CH_3)_3C$). Peak 2 (1.4) was due to **12**, peak 3 (2.1) to an unidentified component, and peak 4 (4.0) to **2**. Yields were determined by using undecane (relative retention time 5.0) as the internal standard.

Reaction of 1-Phenylcyclohexanamine (14). GC analysis (column A, 100 °C) gave two peaks. Peak 1 (relative retention time 1.0) was due to **15** and peak 2 (3.4) to **16**.[3] The yields were calculated by assuming that the crude product consisted only of the compounds (**15** and **16**) for which GC peaks were observed, since the spectra of the crude product were consistent with its being composed mainly of **15** and **16**.

Reaction of 1-Adamantanamine (17). Because of the low solubility of **17** in hexane, the *n*-butyllithium was added to **17** suspended in hexane (5 mL/mmol). A considerable amount of precipitate was present throughout the reflux period. The crude product (92%) exhibited IR and NMR spectra essentially identical with those of **17**.

Reactions of Arylamines. Because of the low solubility of *p*-methoxyaniline and of *o*-(*p*-tolylthio)aniline in hexane, in the reactions of these amines the *n*-butyllithium was added to the amine suspended in hexane. The crude product from each of the reactions exhibited spectra essentially identical with those of the reactant.

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Registry No. **2**, 502-56-7; **6**, 21404-88-6; **7**, 108-88-3; **8**, 35177-30-1; **9**, 629-62-9; **10**, 2922-51-2; **11**, 87012-80-4; **12**, 107-45-9; **13**, 590-50-1; **14**, 2201-24-3; **15**, 108-94-1; **16**, 2626-61-1; **17**, 768-94-5.

Microbial Hydroxylation of Heteroyohimbine Alkaloids

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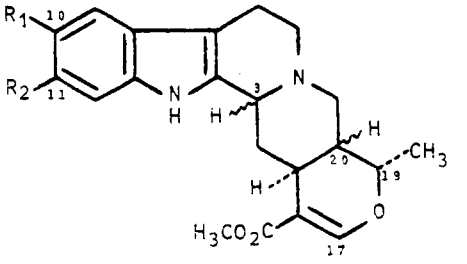
Microbial transformations of therapeutically useful indole alkaloids have been studied extensively over the past several decades to obtain new active derivatives.[1] Surprisingly, less attention has been paid to the widespread naturally occurring heteroyohimbine alkaloids. As the sole example of a potentially reasonably useful process in this class is the regiospecific hydroxylation of ajmalicine (**1a**)



1 R_1, R_2:H 2 R_1:OH, R_2:H 3 R_1:H, R_2:OH

(1) For leading references see: Holland, H. L., In "The Alkaloids"; Rodrigo, R. G. A., Ed.; Academic Press: New York, 1981; Vol. 18, p 323.

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Table I. Microbial Transformation Products

microorganism	yield,[a,d] % 2a	3a	2b	3b	2c	2d	3d
Cunninghamella elegans ATCC 9245	92 (5)		(95)		78 (16)	56 (41)	
Cunninghamella blakesleana ATCC 8688a	27 (48)	18	(97)		65 (29)	49 (45)	
Mucor griseo-cyanus (a)[c]	12 (61)	21	(82)	15	(97)	(95)	
MRRS 10-IBI[b,c]	19 (62)	13	23	72	(95)	(95)	
Streptomyces platensis ATCC 13895	(91)	<5	(96)		(95)	41 (23)	32
Streptomyces rimosus ATCC 10970	(92)	<5	(96)		(93)	13 (75)	<5
Streptomyces rimosus IBI-A6[c]	12 (79)	<5	(95)		(95)	15 (71)	<5

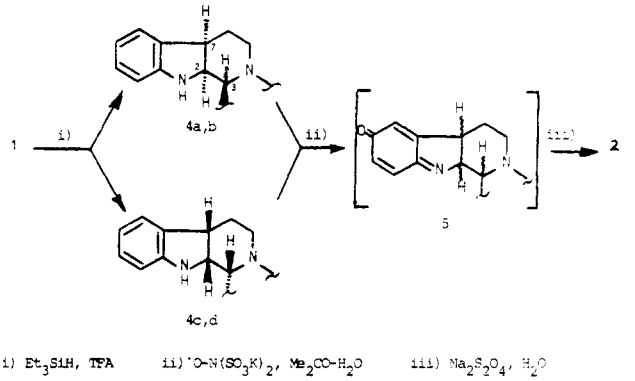
[a] The yields were determined by HPLC analysis; the percent of recovered starting material is give in parentheses. [b] Mold isolated from the rhizosphere of *Rauvolfia vomitoria* (Zaire). [c] From IBI Private Collection. [d] No 3c was obtained in any case.

Table II. ^{1}H NMR Chemical Shifts at 200 MHz of Aromatic Protons for 2 and 3[a]

compd	chemical shift, δ H-9	H-10	H-11	H-12
2a[b]	6.69[d]		6.54[f]	7.09[e]
2b[c]	6.78[d]		6.68[f]	7.04[e]
2c[c]	6.98[d]		6.80[f]	7.27[e]
2d[c]	6.84[d]		6.72[f]	7.13[e]
3a[b]	7.21[e]	6.58[f]		6.80[d]
3b[c]	7.15[e]	6.58[f]		6.69[d]
3d[b]	7.23[e]	6.49[f]		6.76[d]

[a] Data for other protons are given in the Experimental Section. [b] In Me_2SO-d_6. [c] In $CDCl_3$. [d] Doublet (J = 2.0 Hz). [e] Doublet (J = 8.5 Hz). [f] Doublet of doublets (J = 8.5, 2.0 Hz).

Scheme I



by *Gongronella urceolifera* to **2a** which exhibited an increased anticonvulsant activity relative to its unhydroxylated counterpart.[2] In light of the improved biological properties conferred by aromatic hydroxylation, we decided to investigate the microbial transformations of the four heteroyohimbine stereoisomers, namely, **1a**, tetrahydroalstonine (**1b**), isoajmalicine (**1d**), and akuammigine (**1d**). Over 100 microorganisms known for their ability to metabolize several classes of indole alkaloids, steroids, and antibiotics were screened, and, of these, seven were selected (Table I) for preparative-scale fermentations.

Each of the isolated metabolites showed the molecular ion at m/z 368 ($C_{21}H_{24}N_2O_4$ by high-resolution mass spectrum), 16 mass units higher than the starting materials, and the presence of the diagnostically useful fragments at m/z 200 ($C_{12}H_{12}N_2O$), 186 ($C_{11}H_{10}N_2O$), and 185 ($C_{11}H_9N_2O$) was consistent with structures in which hydroxylation has occurred on the aromatic ring. In the 200-MHz ^{1}H NMR spectra of **2** and **3**, the aromatic protons may be analyzed as an AMX pattern (J_{AM} = 8.5 Hz, J_{MX} = 2.0 Hz, J_{AX} = 0 Hz), typical for the 10- and 11-substitution. The classification of metabolites **2** and **3** to one of the above structural groups as well as the stereochemical integrity vs. the starting material was achieved simply according to ^{1}H and ^{13}C NMR data (Tables II and III). Theoretical considerations and experimental data[3] show that in 11-hydroxy derivatives the two ortho protons (H-10, H-12) have a larger difference in chemical shifts than that between H-9 and H-11 in 10-OH compounds. Furthermore, the assigning of the aromatic carbons was made from known chemical shift theory, from additivity rules, and from single-frequency off-resonance decoupling (SFORD) experiments and is in accord with the assignments reported for suitable model compounds. An hydroxy group shifts a para carbon 5–7 ppm to higher field and an ortho carbon 10–15 ppm in the same direction while the ipso carbon usually moves 30 ppm downfield. Comparison of the aromatic shifts in **2** and **3** with those in the corresponding precursors led to the structures of 10-OH derivatives for **2a–d** and 11-OH compounds for **3a–d**, respectively.

The structures of **2** were also confirmed by an independent way. The isomerically pure (checked by ^{13}C NMR) 2,7-dihydroindoles **4**, available by ionic hydrogenation of **1** with triethylsilane in neat trifluoroacetic acid,[4] were subjected to regiospecific 10-hydroxylation via the agency of potassium nitrosodisulfonate (Fremy's salt)[5] and subsequent reduction of the transient indoline *p*-quinone imides **5** with sodium hydrosulfite (Scheme I). Assignment of stereochemistry for the hitherto unknown **4** was by examination of IR data (presence of Bohlmann–Wenkert bands[6] for *trans*-quinolizidines) and spin–spin coupling constants[7] ($J_{2,7}$ = 6.6–7.0 Hz, $J_{2,3}$ = 2.4–2.9 Hz) in the ^{1}H NMR spectra, and the observed stereochemical control by the chirality at the position adjacent to the indole moiety (C-3) presumably reflects stereoelectronic effects.[8]

Interestingly, the mold isolated by us from the roots of the alkaloid-bearing plant *Rauvolfia vomitoria* and named MRRS 10-IBI hydroxylates tetrahydroalstonine (**1b**) in high yield but fails to metabolize the closely related alkaloids **1c** and **1d**. The remarkable feature of the microbial oxygenation reaction by this mold is the unprecedented

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(6) Crabb, A. T.; Newton, R. F.; Jackson, D. *Chem. Rev.* **1971**, *71*, 109.
(7) Booth, H.; Masamune, T. J. *J. Chem. Soc., Perkin Trans 2*, **1972**, 354.
(8) A related reduction of octahydroindolo[2,3-*a*]quinolizine with $NaBH_4$–TFA has also been reported by Gribble to occur with the same stereochemical outcome (Gribble, G. W.; Johnson, J. L.; Saulnier, M. G. *Heterocycles* **1981**, *16*, 2109).

Table III. ^{13}C NMR Chemical Shifts of Aromatic Carbons at 50.2 MHz for 2 and 3

compd	chemical shift[a]							
	C-2	C-7	C-8	C-9	C-10	C-11[d]	C-12[d]	C-13
2a[b]	135.6	105.5	127.3	101.7	150.2	110.2*	114.4*	131.2
2b[c]	135.7	107.6	128.0	102.9	149.6	110.7*	111.4*	131.2
2c[c]	133.3	106.6	128.2	102.7	149.6	110.9*	111.7*	130.8
2d[b]	134.0	106.3	128.0	103.0	149.9	111.2*	111.7*	131.2
3a[b]	133.0	106.8	120.7	117.7	108.7	152.3	97.1	137.2
3b[c]	133.0	108.9	121.1	118.4	109.3	152.0	97.2	137.0
3d[b]	132.2	105.5	120.3	117.4	108.3	152.3	96.8	130.7

[a] In parts per million downfield from Me_4Si. [b] In Me_2SO-d_6. [c] In $CDCl_3$. [d] Asterisked values may be interchanged.

regioselective 11-hydroxylation, a reaction that is difficult to achieve by chemical means without affecting the other sites of the molecule.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 681 spectrophotometer, ultraviolet spectra (in EtOH) were obtained on a Perkin-Elmer 554 UV–vis spectrophotometer, and ^1H NMR spectra and ^{13}C NMR spectra were obtained on a Varian XL-200. Mass spectra (EI) were recorded on Varian 112 (Model 212 for high-resolution spectra). Thin-layer chromatography (TLC) was performed on silica gel GF_{254} (Merck) in ethyl acetate–propan-2-ol–NH_3 (96:4:2) as the eluant and visualized by spraying with Fast Blue B salt solution; the color of the spots are given. High-pressure liquid chromatography was performed with a Hewlett-Packard 1084 A instrument equipped with variable-wavelength detector, and retention times (t_R) in minutes are reported. Separations were obtained with the following systems: (I) Lichrosorb RP8 (10 μm, Merck), 250 × 3 mm, flow rate 2 mL/min, eluants (a) MeCN–MeOH (40:60) or (b) MeCN–phosphate buffer (0.05%, pH 4.5) (75:25); (II) Lichrosorb Si 100 (10 μm, Merck) 250 × 3 mm, flow rate 2 mL/min, $CHCl_3$–MeOH (95:5). Alkaloids **1a–d** were purchased from Inverni della Buffa, Milan. Unless noted otherwise (see Table I) all microorganisms were obtained from the American Type Culture Collection (ATCC), Rockville, MD.

Fermentation Procedure. The screening was performed by a two-stage fermentation procedure. The first stage was a 75-h culture of the microorganism in 550-mL Erlenmeyer flasks filled with 50 mL of medium A (corn steep liquor, 0.2%; dextrose, 0.4%; $(NH_4)_2SO_4$, 0.1%; KH_2PO_4, 0.6%; $CaCO_3$, 0.5%) and shaken on a rotatory shaker at 200 rpm and at 28 °C and this was used to inoculate the second-stage Erlenmeyer flasks containing 50 mL of medium B (corn-steep liquor, 0.2%; glucose, 0.2%; $(NH_4)_2SO_4$, 0.1%; Na_2HPO_4, 0.15%; $CaCO_3$, 0.05%). After 24 h of incubation at 28 °C and 200 rpm, a sterile water solution of the substrate as the hydrochloride was added (200 mg/L of culture medium). The conversion was monitored by TLC. Samples 24, 72, and 144 h after substrate addition, adjusted to pH 8 with NH_4OH, were extracted with ethyl acetate and analyzed by TLC. Controls were substrates in sterilized medium and cultures without substrates under the usual fermentation conditions. Preparative fermentations were performed with the same procedure in 1-L Erlenmeyer flasks or in a 12-L laboratory fermentor equipped with a mechanical stirrer, thermostat, sterile air inlet, and pH probe. The conversion was allowed to proceed for 72 to 144 h and was monitored at 24-h intervals by TLC or HPLC. The cultures were finally harvested and twice extracted at pH 7.8 with ethyl acetate. The organic extracts were evaporated to dryness under vacuum.

Transformation Products. 10-Hydroxyajmalicine (2a): mp 256–259 °C dec (AcOEt) (lit.[2] mp 285 °C); R_f 0.37 (violet); UV λ_{max} 228, 279, 295 (sh), 310 (sh) nm (log ε 4.30, 3.93); IR ($CHCl_3$) 3490, 3320, 1690, 1620 cm^{-1}; mass spectrum (180 °C), m/z (relative intensity) 368 (M^+·, 100), 367 (77), 353 (18), 200 (39), 186 (22), 185 (18); ^1H NMR (Me_2SO- d_6) δ 10.42 (1 H, s, OH), 7.46 (1 H, s, H-17), 4.43 (1 H, q, J = 7.0 Hz, H-19), 3.74 (3 H, s, CO_2CH_3), 1.16 (3 H, d, J = 7.0 Hz, H-18); t_R (II) 1.94.

10-Hydroxytetrahydroalstonine (2b): R_f 0.56 (violet); UV λ_{max} 228, 280, 294 (sh), 310 (sh) nm (log ε 4.28, 3.95); IR ($CHCl_3$) 3470, 3420, 1690, 1630 cm^{-1}; mass spectrum (160 °C), m/z (relative intensity) 368 (M^+·, 100), 367 (67), 353 (20), 200 (81), 186 (9), 185 (10); ^1H NMR ($CDCl_3$) δ 8.89 (1 H, s, OH), 7.80 (1 H, br, s, NH), 7.50 (1 H, s, H-17), 4.50 (1 H, dq, J = 12.0, 6.3 Hz, H-19), 3.73 (3 H, s, CO_2CH_3), 1.38 (3 H, d, J = 6.3 Hz, H-18); t_R (Ib) 3.36.

10-Hydroxyisoajmalicine (2c): mp 159–161 °C dec (EtOAc); R_f 0.22 (violet); UV λ_{max} 228, 282, 300, 313 nm; mass spectrum (170 °C), m/z (relative intensity) 368 (M^+·, 67), 367 (45), 200 (48), 185 (13), 172 (100); ^1H NMR ($CDCl_3$) δ 8.76 (1 H, br s, NH), 7.56 (1 H, s, H-17), 5.1 (1 H, m, OH), 4.57 (1 H, br s, $W_{1/2}$ = 8 Hz, H-3), 4.36 (1 H, dq, J = 6.3, 3.0 Hz, H-19), 0.91 (1 H, d, J = 6.3 Hz, H-18); t_R (II) 4.36.

10-Hydroxyakuammigine (2d): mp 128–130 °C (AcOEt); R_f 0.29 (violet); UV λ_{max} 224, 281, 300, 315 nm; IR (Nujol) 3320, 1680, 1625 cm^{-1}; mass spectrum (200 °C), m/z (relative intensity) 368 (M^+·, 100), 367 (67), 353 (77), 200 (17), 186 (14), 185 (23), 172 (50); ^1H NMR ($CDCl_3$) δ 8.44 (1 H, s, NH), 7.61 (1 H, s, H-17), 4.45 (1 H, dq, $J_{18,19} \simeq J_{19,20}$ = 6.5 Hz, H-19), 3.78 (3 H, s, CO_2CH_3), 1.25 (3 H, d, J = 7.0 Hz, H-18); t_R 3.20. Anal. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.45; H, 6.56; N, 7.60. Found: C, 68.43; H, 6.54; N, 7.70.

11-Hydroxyajmalicine (3a): R_f 0.42 (brown); UV λ_{max} 234, 270, 298, 310 nm (log ε 4.15, 3.78, 3.60, 3.51); IR (Nujol) 3315, 1680, 1630 cm^{-1}; mass spectrum (180 °C), m/z (relative intensity) 368 (M^+·, 100) 367 (72), 353 (12), 200 (35), 186 (22), 185 (14), 172 (71); ^1H NMR (Me_2SO-d_6) δ 10.38 (1 H, s, OH), 9.13 (1 H, br s, NH), 7.53 (1 H, s, H-17), 4.46 (1 H, dq, J = 6.5, 3.0 Hz, H-19), 3.73 (3 H, s, CO_2CH_3), 1.13 (3 H, d, J = 6.5 Hz, H-18); t_R (II) 2.06.

11-Hydroxytetrahydroalstonine (3b): R_f 0.52 (brown); UV λ_{max} 234, 272, 298, 308 nm; IR ($CHCl_3$) 3450, 1690, 1625 cm^{-1}; mass spectrum (150 °C), m/z (relative intensity) 368 (M^+·, 100), 367 (73), 353 (25), 200 (76), 186 (11), 185 (19); ^1H NMR ($CDCl_3$) δ 8.74 (1 H, s, OH), 8.03 (1 H, s, NH), 7.50 (1 H, s, H-17), 4.50 (1 H, dq, J = 6.3, 12.0 Hz, H-19), 3.73 (3 H, s, CO_2CH_3), 1.38 (3 H, d, J = 6.3 Hz, H-18); t_R (Ib) 3.82.

11-Hydroxyakuammigine (3d): R_f 0.33 (brown); UV λ_{max} 232, 269, 298, 310 nm; IR (Nujol) 3315, 1685, 1630 cm^{-1}; mass spectrum (180 °C), m/z (relative intensity) 368 (M^+·, 100), 367 (85), 353 (77), 200 (81), 185 (10); ^1H NMR (Me_2SO-d_6) δ 10.30 (1 H, s, NH), 7.48 (1 H, s, H-17), 4.34 (1 H, dq, $J_{19,20} \simeq J_{18,19}$ = 7.0 Hz, H-19), 3.71 (3 H, s, CO_2CH_3), 1.25 (3 H, d, J = 7.0 Hz, H-18); t_R (Ia) 4.09.

Conversion of Heteroyohimbines 1 into the Corresponding 10-Hydroxy Derivatives 2. General Procedure. (a) A solution of 500 mg (1.42 mmol) of **1** in 5 mL of trifluoroacetic acid under nitrogen was cooled at 0 °C, and 1.13 mL (7.10 mmol) of triethylsilane was added. The reaction mixture was allowed to warm slowly at room temperature overnight, diluted with 200 mL of water, basified with concentrated ammonia and extracted with ethyl acetate. After the mixture was dried (Na_2SO_4) and the solvent evaporated, the crude 2,7-dihydroindole was purified by flash chromatography (silica gel) to give pure **4** (orange stain with 10% ceric ammonium sulfate in 85% H_3PO_4).

(b) A solution of **4** (200 mg, 0.56 mmol) in 5 mL of purified acetone was added dropwise to a solution of potassium nitrosodisulfonate (Fremy's salt; 450 mg, 1.68 mmol) in 50 mL of water–acetic acid (95:5). After 24 h, sodium hydrosulfite was added to discharge the lilac color. The resulting pale yellow solution was diluted with ice cold aqueous ammonia and extracted with ethyl acetate. The combined organic layers were washed, dried, and evaporated to afford, after chromatography, the pure **2** in 40–55% range yield, identical in all respects with the sample isolated from the microbial transformations.

(2*S*,7*R*)-2,7-Dihydroajmalicine (4a): 85% yield; UV λ_{max} 230, 247, 298 nm; IR ($CHCl_3$) 3380, 2810, 2770, 1695, 1615 cm^{-1};

mass spectrum (150 °C), m/z (relative intensity) 354 (M^{+}·, 100), ^1H NMR (Me_2SO-d_6) δ 6.12 (1 H, s,NH); 3.50 (1 H, dd, J = 6.6, 2.4 Hz, H-2); ^{13}C NMR (Me_2SO-d_6) 62.8 and 62.3 (C-2, C-3), 41.2 (C-7).

(2*S*,7*R*)-2,3,4,5,6,7-Hexahydroalstonine (4b): 79% yield; ^1H NMR (Me_2SO-d_6) 7.48 (1 H, s, H-17), 5.42 (1 H, m, NH), 4.38 (1 H, dq, J = 6.5, 12.0 Hz, H-19), 3.62 (3 H, s, CO_2CH_3), 3.42 (1 H, dd, J = 6.6, 2.4 Hz, H-2), 1.29 (3 H, d, J = 6.5 Hz, H-18).

(2*R*,7*S*)-2,7-Dihydroisoajmalicine (4c): 54% yield; ^1H NMR (Me_2SO-d_6) δ 5.46 (1 H, br s, NH), 3.45 (1 H, dd, J = 6.8, 2.7 Hz, H-2); ^{13}C NMR (Me_2SO-d_6) 62.1 (C-2), 53.3 (C-3), 41.2 (C-7).

(2*R*,7*S*)-2,7-Dihydroakuammigine (4d): 59% yield; IR ($CHCl_3$) 3380, 2830, 2775, 1695, 1615 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 5.65 (1 H, br s, NH), 3.32 (1 H, dd, J = 7.0, 2.9 Hz, H-2); ^{13}C NMR ($CDCl_3$) 63.4 (C-2), 57.6 (C-3), 40.3 (C-7).

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Registry No. **1a**, 483-04-5; **1b**, 6474-90-4; **1c**, 483-03-4; **1d**, 642-17-1; **2a**, 36104-59-3; **2b**, 86940-56-9; **2c**, 86940-57-0; **2d**, 86940-58-1; **3a**, 73232-42-5; **3b**, 86940-59-2; **3d**, 86940-60-5; **4a**, 86940-61-6; **4b**, 86940-62-7; **4c**, 86940-63-8; **4d**, 86940-64-9.

Further Characterization of the 1,1-Diphenyl-2,2-dimethylpropyl Radical

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Introduction

Recently[1] we have had occasion to examine in some detail the mechanism of that abnormal version of the Finkelstein reaction that leads to coupled products rather than the expected alkyl iodides. These reactions go via carbocation intermediates that are either reduced directly by iodide to free radicals or form transient covalent iodides. Thus, triphenylmethyl chloride reacts with sodium iodide in acetone to give a complex mixture that clearly displays the proton NMR of the triphenylmethyl dimer. In contrast, 1,1-diphenyl-2,2-dimethylpropyl chloride reacts under similar conditions to form 1,1-diphenyl-2,2-dimethylpropane and 2,3-diphenyl-3-methyl-1-butene in equal amounts. Both products arise through the intermediate 1,1-diphenyl-2,2-dimethylpropyl cation.

Anticipating the formation of the 1,1-diphenyl-2,2-dimethylpropyl free radical in the above reaction, we felt that an examination of this radical and its dimer products would be worthwhile. First reported by Schlenk and Racky,[2] the radical was initially reported to form a dimer that did not dissociate like that of triphenylmethyl. Subsequently, Conant and Bigelow[3] suggested that this observation was erroneous. They prepared the radical by the method of Ziegler by first generating the corresponding anion from the chloride and sodium amalgam. Oxidation of the anion to the radical was achieved with the tetramethylethylene dibromide (TMEDB). The radical dimerized reversibly and reacted with oxygen in contrast to the report of Schlenk and Racky. More recently, Lorand and Wallace[4] published the electron spin resonance (ESR) spectrum of the radical generated by the thermal decomposition of *tert*-butyl 2,2-diphenyl-3,3-dimethylperbutanoate. No detailed analysis was made beyond the assignment of the hyperfine couplings to the methyl protons as 0.24 G.

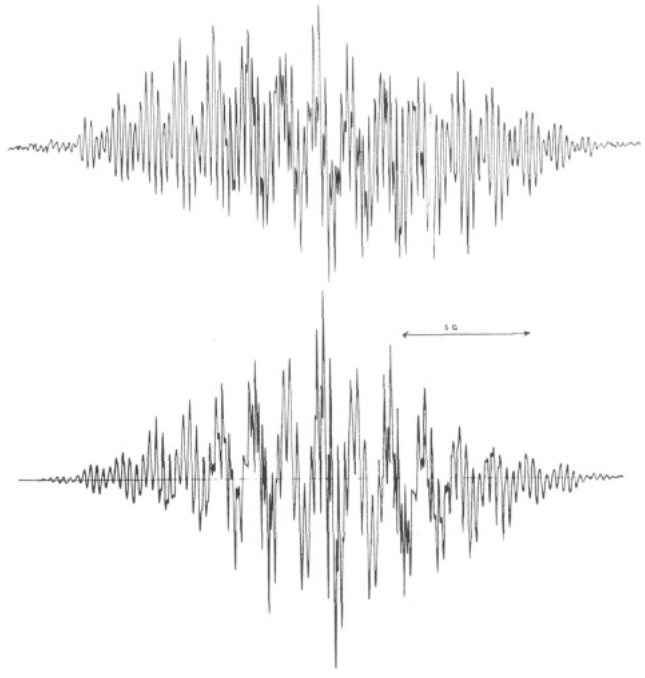

Figure 1. The ESR spectrum of the 1,1-diphenyl-2,2-dimethylpropyl radical (upper) and the computer simulation of same (lower).

Results and Discussion

The 1,1-diphenyl-2,2-dimethylpropyl radical was generated under nitrogen directly in the ESR tube by the addition of an ether solution of the corresponding anion to TMEDB. The spectrum is shown in Figure 1 as is the computer-simulated spectrum. Since the spectrum can theoretically contain up to 750 lines, the fitting is not a trivial matter. Working with information derived from the wings of the spectrum and judgments from related structures, the best set of hypefine coupling constants was found to be a_H^o = 2.6, a_H^m = 1.3, a_H^p = 2.7, and a_H^{Me} = 0.24 G, respectively. Only the absolute magnitude of the meta coupling can be derived from the experimental spectrum though it may be presumed to be negative in sign as in other benzyl-like systems. Changes in these by as little as +0.05 G produced marked changes in the central portion of the spectrum where many overlapping lines occur. The ring couplings are estimated to be good to ±0.1 G and the couplings to the methyl protons to ±0.02 G.

The ESR parameters of diphenylmethyl and fluorenyl radicals have been determined and compared previously.[5,6] The α-hydrogen coupling constants (14.7 and 13.9 G, respectively) have been intepreted as indicating a high degree of planarity and electron delocalization in the diphenylmethyl system. A similar conclusion can be drawn from

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