Acknowledgments.—The authors wish to thank J. V. Pustinger, Jr., and J. Strobel of Monsanto Research Corp. for obtaining the F^{19} nmr spectra and J. R. Boal of Mellon Institute for obtaining the mass spectra reported in this work.

The Degradation of (−)-4-Methylisopulegone to (+)-2-Isopropyl-2-methylsuccinic Acid[1]

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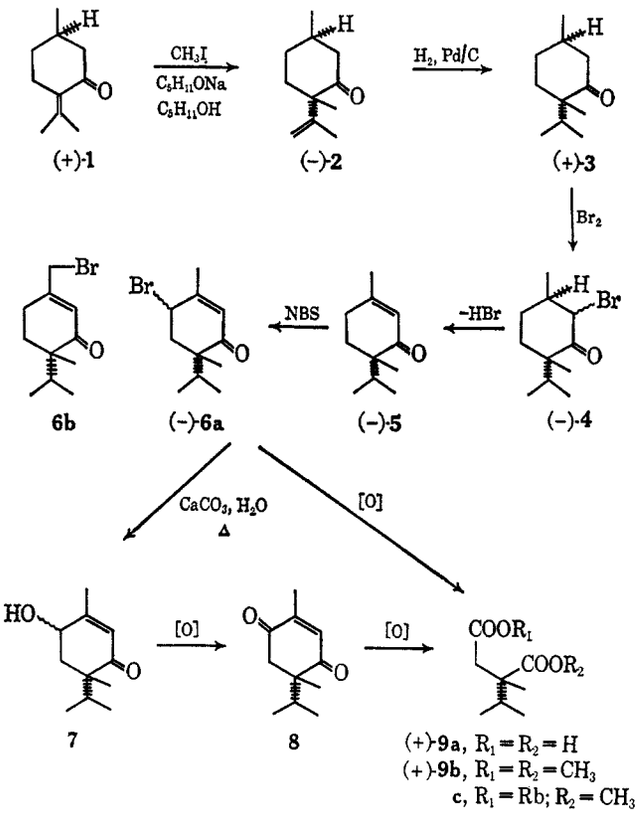
The conversion of (−)-4-methylisopulegone [(−)-4-methyl-*p*-menth-8(9)en-3-one)] (**2**) into (+)-2-isopropyl-2-methylsuccinic acid (**9a**) and the structures of the intermediate products are reported. The absolute configuration of **2** has been unequivocally established by X-ray crystallography of the rubidium salt of the half-methyl ester of (+)-2-isopropyl-2-methylsuccinic acid (**9c**). The acid **9a** is important since it is a degradation product of several terpenes,[3] including (+)-camphor,[4] (+)-thujone,[5] and (+)-sabinene,[6] and has been used to establish the absolute configuration of these and related molecules. We had previously arrived at an incorrect assignment of the absolute configuration of **2** through a quasi-racemate study involving (+)-2-isopropyl-2-methylglutaric acid (**11a**) and (+)-2-isopropylglutaric acid. Since quasi-racemate formation was observed between these acids, we had concluded that the isopropyl groups of these two molecules should have opposite configurations.[7] The paucity of material at that time prevented degradation to 2-isopropyl-2-methylsuccinic acid of known absolute configuration.[8] We have devised and now report a successful degradation of **2** which provides enough **9a** for complete characterization and optical rotation studies.

The reaction sequence used in the degradation is shown in Scheme I, which includes the alkylation of (+)-pulegone (**1**) to (−)-**2**. The latter was isolated and purified as previously reported.[7a] The structure of **2** was confirmed by ir, mass, nmr, and uv spectral data. Catalytic hydrogenation of **2** afforded the expected (+)-4-methyl-*p*-menth-3-one (**3**). Its conversion into the unsaturated ketone **5** *via* the crystalline bromo ketone **4** was also accomplished.[7a]

SCHEME I



All previous attempts at degrading the unsaturated ketone **5** to **9a** failed. We therefore sought a degradation route in which we could activate or substitute C-4 of the unsaturated ketone **5** in such a way that 2-isopropyl-2-methylsuccinic acid could be obtained. Allylic bromination of **5** with N-bromosuccinimide in carbon tetrachloride yielded an unsaturated bromo ketone. This bromination product might be **6a** or **b**. The structure **6a** was apparent from the nmr spectrum, which shows a sharp singlet at τ 8.15 (3 H) due to a vinylic methyl group, whereas the parent ketone **5** shows this methyl signal at 8.10 (3 H). The shift is attributed to the inductive effect exerted by the bromide substituent. The absence of absorption due to allylic methylene protons in the τ 7.5–8.0 region and the survival of the methyl group during bromination provide convincing evidence that structure **6a** is correct. Additional evidence for the formation of a monobromination product is gained from the bromine analysis. Oxidation of **6a** with alkaline potassium permanganage gave **9a**, mp 128–130°, $[\alpha]^{24}D$ +15° (*c* 0.8, C_2H_5OH). A mixture of **9a** obtained from the degradation with an authentic sample of (+)-**9a** showed no depression in melting point.[9] The infrared spectra of these samples were identical, and the mass fragmentation patterns of **9a** and **9b** confirm the structure assignment to **9a**.

(1) (a) This study was initiated before the X-ray crystallography studies were published.[1b] (b) M. R. Cox, H. P. Koch, W. B. Whalley, M. B. Hursthouse, and D. Rogers, *Chem. Commun.*, 212 (1967).

(2) (a) M. V. Kulkarni, Ph.D. Thesis, Oklahoma State University, Stillwater, Okla., May 1967. (b) Address correspondence and reprint requests to this author.

(3) L. Ahlquist, J. Asselineau, C. Asselineau, K. Serck-Hanssen, S. Stallberg-Stenhagen, and E. Stenhagen, *Ark. Kemi*, **14**, 171 (1959).

(4) J. Porath, *ibid.*, **1**, 525 (1950).

(5) H. E. Smith, and A. W. Gordon, *J. Amer. Chem. Soc.*, **84**, 2840 (1962).

(6) T. Norin, *Acta Chem. Scand.*, **16**, 640 (1962).

(7) (a) E. J. Eisenbraun, F. Burian, J. Osiecki, and C. Djerassi, *J. Amer. Chem. Soc.*, **82**, 3476 (1960); (b) A. Fredga, *Tetrahedron*, **8**, 126 (1960).

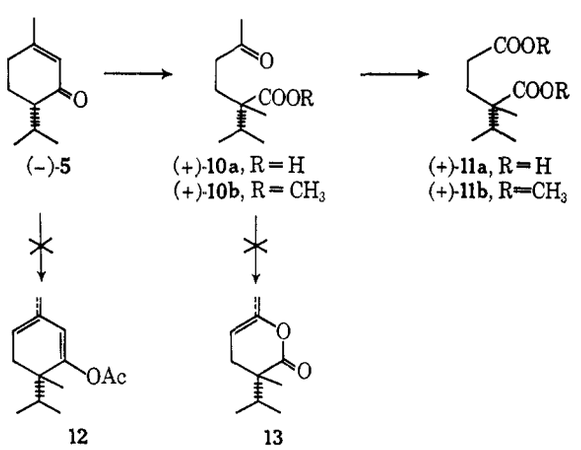
(8) J. Porath, *Ark. Kemi*, **1**, 385 (1949); (b) W. von E. Doering, M. R. Willcott, and M. Jones, *J. Amer. Chem. Soc.*, **84**, 1224 (1962); (c) J. D. Edwards, Jr., and N. Ichikawa, *J. Org. Chem.*, **29**, 503 (1964).

(9) We are grateful to Dr. H. E. Smith for a sample of (+)-**9a**.

The nmr and ir spectra of **9b** support its structure. Comparison of **9b** with the methyl ester of authentic **9a** through gas chromatography on a Carbowax 20M column showed these materials to be homogeneous and indistinguishable. It is assumed that oxidation of **6a** to **9a** proceeds through 4-hydroxy-6-isopropyl-3,6-dimethyl-2-cyclohexen-1-one (**7**), since **7** may be prepared by treating **6a** with a refluxing suspension of aqueous calcium carbonate. The crude product **7** was oxidized with alkaline potassium permanganate and gave, as expected, (+)-2-isopropyl-2-methylsuccinic acid (**9a**).[1b,6]

The degradation route described in Scheme I is deceptively simple but was used only after several other attempts at the degradation of the unsaturated ketone **5** beyond (+)-2-isopropyl-2-methyl-5-oxocaproic acid (**10a**) or **11a** had failed. These attempts included formation of the enol acetate **12** and the enol lactone **13** as shown in Scheme II.

SCHEME II



We believe that these molecules were formed but that reaction conditions necessary for their formation were too severe to permit the products to survive to isolation. The evidence for enol lactone formation was the elimination of water on pyrolysis of **10a** and also the observation of enol lactone carbonyl bands in the infrared spectrum of the pyrolysis product of **10a**. Reaction of the α,β-unsaturated ketone **5** with isopropenyl acetate catalyzed with *p*-toluenesulfonic acid afforded acetone as expected. Gas chromatographic analysis showed eight peaks and, since materials were limited, a pure enol acetate was not obtained. Therefore, these reactions were abandoned in favor of those in Scheme I. During the course of these studies, we repeated the preparation of **10a,b** and **11a,b**, and confirmed the earlier findings regarding the properties of these molecules; in addition, we report nmr and mass spectral data for **10b** and **11b**.

Experimental Section[10]

Isolation and Purification of (+)-Pulegone (1).—Distillation fractions from oil of pennyroyal[11] boiling at 72–75° (0.7 mm) and 75–80° (0.7 mm) were combined and purified by preparative gas chromatography at 180° using a column packed with Chromosorb W coated with LAC-4R-886. Pulegone (**1**) was obtained in 98.7% purity: bp 74–75° (0.7 mm); $\alpha^{24}D$ +23° (neat) [lit.[12] bp 117° (27 mm), $\alpha^{27}D$ +23.6° (neat)]; $\lambda_{max}^{C_2H_5OH}$ 251 mμ (ε 7370). Its nmr spectrum in CCl_4 showed absorption at τ 9.0 (3 H, d), 8.7 (1 H, d), 8.0 (6 H, s), 8.1 (4 H, s), and 7.6 (2 H, m).

Preparation of (−)-4-Methylisopulegone (2).—The methylation of 106 g of **1** was carried out as described[12] to give 90 g of crude product. Purification by distillation, preparation of its semicarbazone, recrystallization of the semicarbazone to yield 26 g of material melting at 200–202°, and regeneration by steam distillation in the presence of 52 g oxalic acid yielded 15 g of **2**: bp 89–93° (12 mm); $\alpha^{24}D$ −123° (neat); λ_{max}^{EtOH} 294 mμ (ε 51); $\lambda_{max}^{CCl_4}$ 3000, 1720, 1650, 1560, 1470, and 1390 cm^{-1}; nmr (CCl_4), τ 5.05 (2 H, d), 7.3 to 8.2 (6 H, m), 8.3 (3 H, s), 8.7 (1 H, d), 8.9 (3 H, s), and 9.0 (3 H, d). Its mass spectrum showed ion peaks *m/e* 41 (8.2%), 123 (7.7%), 39 (6.0%), 67 (5.4%), 27 (4.4%), and 81 (4.2%) and a parent ion peak *m/e* 166 (2%).

Preparation of (+)-4-Methyl-*p*-menth-3-one (3).—Catalytic hydrogenation of 14 g of **2** as previously described[12] in the presence of 1 g of 10% Pd/C catalyst in 150 ml of 95% ethanol resulted in the uptake of 1 equiv of hydrogen within 45 min. The catalyst was filtered out and the solvent was evaporated and distilled to give 10 g of **3**: bp 85–88° (23 mm); $\alpha^{24}D$ +19° (neat); $\lambda_{max}^{CCl_4}$ 2825, 1710, 1450, and 1375 cm^{-1}; nmr (CCl_4), τ 9.2 (3 H, d), 9.1 (3 H, s), 9.0 (6 H, 2d), 8.4 (1 H, d), 8.2 (1 H, d), 8.0 (2 H, s), and 7.5 to 7.85 (4 H, m). Its mass spectrum showed a molecular ion *m/e* 168 (0.6%), and other prominent, fragments *m/e* 55 (10%), 41 (9.6%), 126 (8.2%), 69 (6.8%), 27 (5.1%), and 43 (4.8%).

Preparation of (−)-2-bromo-6-isopropyl-3,6-dimethylcyclohexanone (4) was carried out as previously described[7a] on 4.6 g of **3** to give 6.2 g of colorless product, bp 140–142° (0.9 mm), which, after recrystallization from *n*-hexane, melted at 79–81°: $[\alpha]^{24}D$ −149° (*c* 1.2; $CHCl_3$); $\lambda_{max}^{CCl_4}$ 1727, 1460, and 1400 cm^{-1}; λ_{max}^{DMSO} 1712 cm^{-1}. There was no shift in the carbonyl-stretching frequency of **3** and **4** when a spectrum taken in DMSO was compared with the corresponding one obtained in CCl_4. The nmr spectrum (in $CDCl_3$) showed bands at τ 9.3 (3 H, s), 9.2 [3 H, 2d (J = 3 cps)], 8.95 [6 H, 2d (J = 5 cps)], 7.6–8.5 (6 H, m), and 4.9 [1 H, d (J = 5 cps)].

Preparation of (−)-6-Isopropyl-3,6-dimethyl-2-cyclohexen-1-one (5).—Dehydrobromination of 1.64 g of **4** as previously described[7a] gave 0.8 g of **5**: $[\alpha]^{24}D$ −81° (*c* 1.4, in $CHCl_3$); λ_{max}^{EtOH} 235 and 320 mμ (log ε 4.12 and 1.85); $\lambda_{max}^{CCl_4}$ 2950, 1665, 1550, 1440, and 1380 cm^{-1}; nmr (CCl_4), τ 9.1–9.3 (9 H, s), 8.8 [1 H, d (J = 3.5 cps)], 8.1 (3 H, s), 7.8 (4 H, m), 4.3 (1 H, s). The mass spectrum showed most intense peaks *m/e* 82 (26.5%), 124 (8.7%), 41 (6.9%), 39 (6.3%), 27 (5.0%), and 109 (3.1%), and a molecular ion *m/e* 166 (0.7%).

(−)-4-Bromo-6-isopropyl-3,6-dimethyl-2-cyclohexen-1-one (6a) was prepared by heating N-bromosuccinimide (1.35 g) and 1 g of **5** in 25 ml of CCl_4 for 1 hr under a nitrogen atmosphere. The hot solution was filtered and the solvent was evaporated. Distillation [bath temperature 85° (1.2 mm)] of the residue gave 0.75 g of **6a**: $[\alpha]^{25}D$ −37° (*c* 1.1, $CHCl_3$); λ_{max}^{DMSO} 1650, 1430, and 1380 cm^{-1}. The nmr spectrum ($CHCl_3$) showed bands at τ 9.25–9.05 (9 H, s), 8.75 [1 H, d (J = 3.5 cps)], 8.15 (3 H, s), 7.8 (2 H, d), and 4.35 (2 H, m). *Anal.* Calcd for $C_{11}H_{17}OBr$: Br, 32.65. Found: Br, 32.47.

4-Hydroxy-6-isopropyl-3,6-dimethyl-2-cyclohexen-1-one (7) was prepared by adding the bromo ketone **6a** (0.5 g) to a stirred suspension of 2 g of calcium carbonate[13] in 20 ml of water; the suspension was boiled for 1 hr, cooled, and extracted with ether. The ether extract was dried with magnesium sulfate, filtered, and concentrated. The viscous liquid (0.250 g) was directly

(10) A Beckman GC-2A or an F & M 700 gas chromatography apparatus was used. The columns, heated at 180–190°, were 10 ft × 0.25 in. and were packed with acid-washed Chromosorb W, 60–80 mesh, coated with LAC-4R-886 or Carbowax 20M. Infrared spectra were obtained with a Beckman IR-5A spectrometer; the nmr spectra were determined in CCl_4 on a Varian A-60 spectrometer using tetramethylsilane as the internal standard (τ 10); abbreviations used are d = doublet, m = multiplet, and s = singlet. Melting points were obtained in open tubes with a Thomas-Hoover apparatus, and are not corrected. The mass spectra were determined at 70 eV on a CEC 21-103C mass spectrometer.

(11) Supplied by Fritzsche Bros., New York, N. Y.

(12) C. Djerassi, J. Osiecki, and E. J. Eisenbraun, *J. Amer. Chem. Soc.*, **83**, 4433 (1961).

(13) S. B. Soloway and F. B. LaForge, *J. Amer. Chem. Soc.*, **69**, 979 (1947).

oxidized with alkaline potassium permanganate without purification. Its spectral properties were $\lambda_{max}^{CCl_4}$ 3400, 2950, 1650, and 1050 cm^{-1}; $\lambda_{max}^{CH_3OH}$ 235 mμ (log ε 4.9); nmr (CCl_4), τ 9.1–9.2 (9 H, s), 8.75 (1 H, d), 8.05 (3 H, s), 7.85 (2 H, d), 6.4 (1 H, s), 6.1 (1 H, s), and 4.35 (1 H, s).

Permanganate Oxidation of 6a to 9a.—The bromo ketone **6a** (0.35 g) was added to 3 ml of 6% NaOH and the mixture was cooled to 10° with an ice water bath. To the cooled solution was added 10 ml of 0.17 *M* $KMnO_4$, the suspension was stirred overnight and filtered, and the filtrate was acidified with dilute HCl and then continuously extracted with ether. The ether layer was dried over $MgSO_4$, filtered, and concentrated. The crude solid product was sublimed at 110° (0.8 mm) to give 150 mg of **9a**. Recrystallization from 95% ethanol gave material melting at 128–130°: $[\alpha]^{24}D$ +15° (*c* 0.8, in ethanol); $[\alpha]_{290}$ +358°, $[\alpha]_{260}$ +345°, $[\alpha]_{248}$ +276°, $[\alpha]_{232}$ +131°, $[\alpha]_{225}$ +508° (*c* 0.16, CH_3OH); CD, $[\theta]_{275}$ +6730, $[\theta]_{217}$ +2977, $[\theta]_{200}$ +4140 (*c* 0.16, CH_3OH). The infrared spectrum of **9a** showed bands at λ_{max}^{KBr} 3000, 1758, 1710, 1440, and 1370 cm^{-1}. The melting point of **9a** was not lowered when it was mixed with an authentic sample.[9] The mass spectrum of **9a** showed an intense peak at *m/e* 69 (18.6%), 41 (16.0%), 84 (9.0%), 39 (8.2%), 27 (6.6%), 43 (5.0%), and 114 (1.8%).

The dimethyl ester **9b**, prepared by treating **9a** with diazomethane, was distilled at bath temperature 128° (2.3 mm): $[\alpha]^{24}D$ +30° (*c* 0.83, $CHCl_3$); ORD as a positive plain curve $[\alpha]_{393}$ +24°, $[\alpha]_{345}$ +78°, $[\alpha]_{290}$ +208° (*c* 0.50, CH_3OH); $\lambda_{max}^{CCl_4}$ 2920, 1743, 1550, 1440, 1360, and 1220 cm^{-1}; nmr (CCl_4), τ 8.7–9.2 (9 H, s), 7.9 [1 H, d (*J* = 3 cps)], 7.45 (2 H, s), and 6.3 (6 H, d). The mass spectrum of **9b** showed prominent peaks at *m/e* 15 (4.4%), 26 (2.7%), 27 (7.5%), 28 (2.6%), 29 (7.6%), 31 (26%), 43 (6.7%), 45 (9.9%), and 46 (4.0%). The molecular ion at *m/e* 202 was not detected.

Permanganate Oxidation of 7.—The oxidation procedure previously described was applied to 150 mg of **7** in 2 ml of 6% NaOH to which was added 5 ml of 0.17 *M* potassium permanganate solution. The reaction gave 70 mg of **9a**, mp 128–130°.

(+)-2-Isopropyl-2-methyl-5-oxocaproic Acid (10a).—The following mass spectral, infrared, and circular dichroism data were obtained for **10a**: *m/e* 43 (9.3%), 55 (8.0%), 27 (6.8%), 83 (6.7%), 41 (6.6%), and 39 (4.5%); $\lambda_{max}^{CCl_4}$ 3050, 1710, 1430, and 1380 cm^{-1}; $[\theta]_{299}$ +231, $[\theta]_{285}$ +297, $[\theta]_{232}$ −264, $[\theta]_{223}$ −99 (*c* 0.31, CH_3OH).

(+)-Methyl 2-Isopropyl-2-methyl-5-oxocaproate (10b).—The following mass spectral, infrared, optical rotatory dispersion, and nmr data were obtained for **10b**: *m/e* 43 (14.1%), 15 (6.0%), 41 (5.9%), 83 (5.7%), and 55 (4.7%); $\lambda_{max}^{CCl_4}$ 2900, 1750, 1720, and 1250 cm^{-1}; $[\alpha]_{400}$ +32°, $[\alpha]_{375}$ +40°, $[\alpha]_{350}$ +56°, $[\alpha]_{325}$ +96°, $[\alpha]_{305}$ +152°, $[\alpha]_{265}$ −134°, and $[\alpha]_{250}$ −28° (*c* 0.60, dioxane); nmr (CCl_4), τ 9.25 (3 H, s), 9.05 (6 H, 2d), 8.30 (1 H, d), 8.20 (2 H, s), 7.95 (3 H, s), 7.80 (2 H, m), and 6.40 (3 H, s).

(+)-2-Isopropyl-2-methylglutaric Acid (11a).—The following mass spectral infrared, and optical rotatory dispersion data were obtained for **11a**: *m/e* 69 (18.6%), 41 (16.0%), 84 (9.0%), 39 (8.2%), 27 (6.5%), and *m/e* 43 (5.0%); λ_{max}^{KBr} 3000, 1758, 1710, 1440, and 1370 cm^{-1}; $[\alpha]_{340}$ +44°, $[\alpha]_{303}$ +56°, $[\alpha]_{245}$ +90° (*c* 0.51, dioxane).

(+)-Dimethyl 2-Isopropyl-2-methylglutarate (11b).—The following mass spectral, infrared, rotatory dispersion, and nmr were obtained for **11b**: *m/e* 43 (14.1%), 15 (6.0%), 41 (5.9%), 83 (5.7%), 55 (4.7%), and 27 (4.0%); $\lambda_{max}^{CCl_4}$ 3000, 1743, 1440, and 1380 cm^{-1}; $[\alpha]_{375}$ +36°, $[\alpha]_{330}$ +52°, and $[\alpha]_{240}$ +144° (*c* 0.8, CH_3OH); nmr (CCl_4), τ 9.1 (3 H, s), 9.0 (6 H, weak s), 7.8–8.4 (5 H, broad m), and 6.4 (6 H, s).

Registry No.—1, 15815-63-1; 2, 5298-65-7; 3, 15815-65-3; 4, 15815-66-4; 5, 15815-67-5; 6a, 15815-68-6; 7, 15815-69-7; 9a, 5033-83-0; 9b, 15815-71-1; 10a, 15815-75-5; 10b, 15815-72-2; 11a, 15815-73-3; 11b, 15815-74-4.

Acknowledgments.—We thank Mr. M. C. Hamming, Continental Oil Co., for mass spectra and Dr. O. C. Dermer for having read the manuscript.

Alternate Precursors in Biogenetic-Type Syntheses. III.[1] A Ring D Indoline Analog of the Aporphine Alkaloids. Indole as the Alkylating Agent in the Friedel–Crafts Reaction

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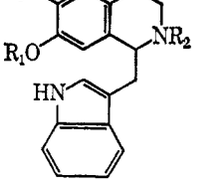
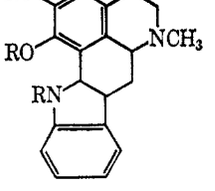
In the first[2] paper of this series we suggested the possible biogenetic conversion of an indole analog of norlaudanosoline into an indole analog of morphine. Since it is well known that norlaudanosoline also can lead to the aporphine alkaloids,[3] the logical development of this theme is the conversion of an indole analog of norlaudanosoline into an indole analog of an aporphine. Chemically, the preferred method of cyclizing the possible biogenetic intermediate **3** seemed to be the alkylation of the benzene ring by the 2,3-double bond of the indole nucleus. Although the alkylation of a benzene ring by an indolenium salt has been described by Harley-Mason and Waterfield,[4] these authors also reported that 1-methyltryptamine and catechol do not react. However, in our case the two reactive centers would be held in a more favorable steric relationship.

The tetrahydroisoquinoline **1** was prepared from N-(3,4-dimethoxyphenethyl)indole-3-acetamide *via* a Bischler–Napieralski cyclization and reduction. Treatment with ethyl formate followed by lithium aluminum hydride reduction converted **1** into its N-methyl derivative (**2**). Strong acid should now bring about hydrolysis of the dimethoxy groups to produce the indole analog of norlandanosoline (**3**) which might



1, $R_1 = CH_3$; $R_2 = H$
2, $R_1 = CH_3$; $R_2 = CH_3$
3, $R_1 = H$; $R = CH_3$



4, R = H
5, R = C(=O)CH_3

well cyclize under the conditions being utilized for hydrolysis. Accordingly, when **2** was refluxed in concentrated hydrobromic acid, the product isolated analyzed for a dihydroxy dihydrobromide indicative of hydrolysis followed by cyclization to **4**, a ring D indoline analog of the aporphine alkaloids. Ultraviolet absorption in acid at 261 mμ (ε 9300), 268 (1300), and 291 (3900) is also consistent[4] with the cyclized compound **4** and not **3**. For further characterization **4** was converted into its triacetyl derivative **5**, whose

(1) For Part II, see G. C. Morrison, R. O. Waite, and J. Shavel, Jr., *J. Org. Chem.*, **32**, 2555 (1967).

(2) G. C. Morrison, R. O. Waite, F. Serafin, and J. Shavel, Jr., *ibid.*, **32**, 2551 (1967).

(3) B. Frank and G. Blasche, *Ann.*, **695**, 144 (1966), and references therein.

(4) J. Harley-Mason and W. R. Waterfield, *Tetrahedron*, **19**, 65 (1963).