Synthesis of 11-Hydroxy-2,3,9,10-tetramethoxy-5,6,13,13a-tetrahydro-8H-dibenzo[*a*,*g*]quinolizine. A Contribution to the Structure of Stepharotine[1]

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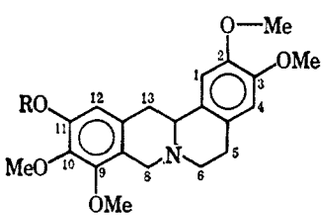
(±)-11-Hydroxy-2,3,9,10-tetramethoxy-5,6,13,13a-tetrahydro-8H-dibenzo[*a*,*g*]quinolizine (**1**) has been prepared by reduction of 11-hydroxy-2,3,9,10-tetramethoxybenzo[*a*]acridizinium bromide (**13**), afforded by hydrobromic acid catalyzed cyclization of quaternary salt **12** formed when 2,3-dimethoxy-4-hydroxybenzyl bromide (**11**) reacts with 6,7-dimethoxyisoquinoline-1-carboxaldoxime. Benzyl bromide **11** was prepared in four steps from the known 2,3-dimethoxy-4-hydroxybenzoic acid **7**. The infrared spectrum of the title compound differs significantly from that of the alkaloid stepharotine.

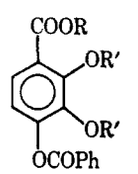
Tomita, Kozuka, and Uyeo[2] have isolated from the root of the *Stephania rotunda Loureiro* a new levorotatory phenolic base to which they have given the name stepharotine. Since stepharotine on methylation with diazomethane gave a product spectroscopically identical with synthetic 2,3,9,10,11-pentamethoxy-5,6,13,13a-tetrahydro-8H-dibenzo[*a*,*g*]quinolizine (**2**) prepared by a modification of the method of Späth and Meinard,[3]



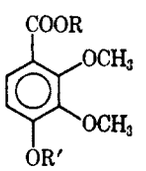
1, R = H
2, R = Me
3, R = Ph

and since phenyl ether **3** on reduction with metallic sodium in liquid ammonia gave a product identified as tetrahydropalmatine, the alkaloid was assigned the structure 11-hydroxy-2,3,9,10-tetramethoxy-5,6,13,13a-tetrahydro-8H-dibenzo[*a*,*g*]quinolizine (**1**). The present communication describes the first synthesis of **1**.

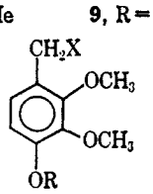
In order to apply the general method developed earlier[4,5] for the synthesis of tetrahydroberberine derivatives, it was necessary to have available the unknown 2,3-dimethoxy-4-hydroxybenzyl bromide (**11**). The most promising starting material appeared to be the 2,3-dimethoxy-4-hydroxybenzoic acid (**7**) of Pascu.[6] Unfortunately, the structure assigned by Pascu to this important compound had been placed in serious doubt by the subsequent work of Critchlow, Haworth, and Pauson,[7] who reported that, like 3,5-diacetoxy-4-benzoxybenzoic acid,[8] Pascu's intermediate, 2,3-diacetoxy-4-benzoyloxybenzoic acid (**4**), when heated with hydrochloric acid underwent not only the expected hydrolysis of the acetoxy groups, but also *ortho* migration of the benzoyl group. This claim was backed by the observation that reacetylation of the hydrolysis product did not lead back to the starting material **4**, and that an elaborate transformation of the hydrolysis product afforded a substituted phthalic acid of a structure explicable only on the basis of rearrangement. These earlier observations, coupled with our own, that the melting point of the dihydroxybenzoxybenzoic acid obtained by hydrolysis of 2,3-diacetoxy-4-benzoyloxybenzoic acid (**4**) was 250–252° instead of 211° as reported by Pascu,[6] or 227° as reported by the British authors,[7] led us to examine as carefully as possible all lines of evidence bearing on the structure of our products.



4, R = H; R′ = Ac
5, R = H; R′ = H
6, R = Me; R′ = Me



7, R = R′ = H
8, R = Me; R′ = H
9, R = Me; R′ = $PhCH_2$



10, X = OH; R = $PhCH_2$
11, X = Br; R = H (not isolated)

Like Pascu we found that our dihydroxybenzoyloxybenzoic acid (**5**) on reacetylation gave back the original diacetoxy compound (**4**). Under no hydrolysis conditions, including those recommended by Critchlow, *et al.*,[7] were we able to obtain a product in which the benzoyl group had migrated. An attempt to decarboxylate our sample of 2,3-dihydroxy-4-benzoyloxybenzoic acid resulted in the evolution of carbon dioxide at 255° and the crude, easily oxidized decarboxylation product was methylated with an excess of diazomethane and subjected to vapor phase chromatography. On a column which could separate authentic samples of 1,2-dimethoxy-3-benzoyloxybenzene and 1,3-dimethoxy-2-benzoyloxybenzene the methylated decarboxylation product of **5** gave evidence (peak matching) of being largely the 1,2-dimethoxy-3-benzoyloxybenzene with no trace of the isomer.

(1) This research was supported by Public Health Service Research Grant No. H-2170 of the National Heart Institute.

(2) M. Tomita, M. Kozuka, and S. Uyeo, *Yakugaku Zasshi*, **86**, 460 (1966); *Chem. Abstr.*, **65**, 10633 (1966).

(3) E. Späth and T. Meinard, *Ber.*, **75**, 400 (1942).

(4) C. K. Bradsher and N. L. Dutta, *J. Amer. Chem. Soc.*, **82**, 1145 (1960).

(5) C. K. Bradsher and N. L. Dutta, *J. Org. Chem.*, **26**, 2231 (1961).

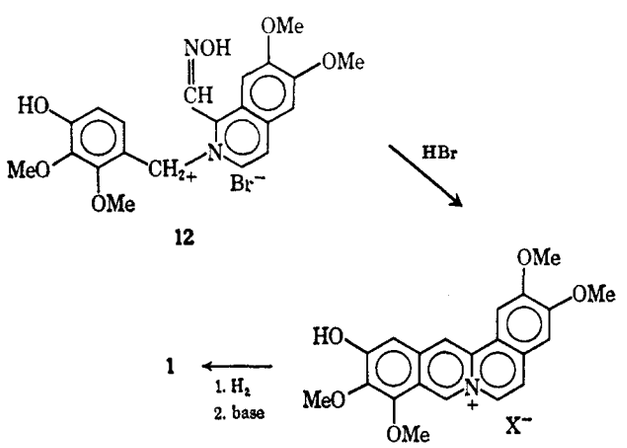
(6) E. Pascu, *Ber.*, **56**, 407 (1923).

(7) A. Critchlow, R. D. Haworth, and P. L. Pauson, *J. Chem. Soc.*, 1318 (1951).

(8) E. Fischer, M. Bermann, and W. Lipschitz, *Ber.*, **51**, 45, 71 (1918).

It seems probable that the significant difference in the melting point of 2,3-dihydroxy-4-benzoyloxybenzoic acid (**5**) observed by us and that reported by Pascu may be a typographical error since good correspondence was found in the physical constants of the dimethyl ether–methyl ester (**6**) and its alkaline hydrolysis product (**7**). The nmr spectrum of hydroxy ester **8** in dimethyl sulfoxide solution was compared with that of its anion according to the directions of Highet and Highet.[9] The base-induced upfield shift of the signals due to the aromatic protons (0.73 and 0.30 ppm) corresponds well with the values reported[9] for one aromatic hydrogen *meta* and one *ortho* to the hydroxyl group, where there is a carbonyl group in the *para* position.

The hydroxy ester was converted in excellent yield into its benzyl ether (**9**) for the lithium aluminum hydride reduction. The reduction product (**10**) was a liquid which could not be distilled, but was obtained analytically pure by chromatography. No method was found for the conversion of the 4-benzyloxy-2,3-dimethoxybenzyl alcohol (**10**) into the corresponding benzyl bromide without simultaneous cleavage of the benzyl ether linkage to afford 2,3-dimethoxy-4-hydroxybenzyl bromide (**11**). Bromide **11** was very unstable and best results were obtained when it was prepared quickly at low temperature by the reaction of hydrogen bromide on alcohol **10**. The crude bromide was allowed to react in anhydrous dimethylformamide with an excess of 6,7-dimethoxyisoquinoline-1-carboxaldoxime[5] affording an over-all yield (from **10**) of the expected quaternary salt **12** of 25%. Cyclization of salt **12** in hydrobromic acid afforded an 84% yield of 11-hydroxy-2,3,9,10-tetramethoxybenzo[*a*]acridizinium bromide (**13**).



Catalytic reduction of **13** over Adams catalyst followed by addition of sodium carbonate afforded 11-hydroxy-2,3,9,10-tetramethoxy-5,6,13,13a-tetrahydro-8H-dibenzo[*a*,*g*]quinolizine (**1**). Methylation of base **1** with diazomethane afforded pentamethoxy derivative **2** identical with an authentic sample prepared by a modification of the directions of Späth and Meinard.[3] Comparison, under the same conditions, of the infrared spectrum of our hydroxy base (**1**) in carbon tetrachloride solution with that of an authentic sample of stepharotine revealed that the two samples are not spectroscopically identical. It is not remarkable that our racemic product **1**, mp 190–192°, should be higher melting than the optically active stepharotine, but it does appear significant that the supposedly pure stepharotine base should be so low melting that it has never been obtained in a crystalline form. An impurity in natural stepharotine might be responsible for the observed differences in ir spectra or the natural product may have a structure other than **1**.

While the structure of our hydroxy base (**1**) could be regarded as demonstrated by the synthetic method used, additional support is afforded by physical evidence. Our hydroxy base (**1**), when heated in dimethyl sulfoxide containing deuterium chloride in deuterium oxide, undergoes exchange of one aromatic hydrogen which must therefore be either *ortho* or *para* to the hydroxyl group.[10] Since the upfield shift (0.22 ppm) observed when hydroxy base **1** was converted into the anion[9] is so small, the possibility that there is an aromatic proton *para* to the hydroxyl group could be eliminated.

Experimental Section[11]

2,3-Dihydroxy-4-benzoyloxybenzoic acid (**5**) was made by hydrolysis of 2,3-acetoxy-4-benzoyloxybenzoic acid[6] as described by Pascu.[6] Since the melting point observed, 250–252°, was significantly higher than previously reported (lit.[6] mp 210–211°) the product was submitted for elemental analysis.

Anal. Calcd for $C_{14}H_{10}O_6$: C, 61.31; H, 3.67. Found: C, 61.31; H, 3.64.

Even when the specific directions of Critchlow, Haworth, and Pauson[7] were followed, only the product reported above was obtained and no isomeric acid, mp 227°, was found. Also in contrast to the report of the British authors[7] we found that reacetylation of the product, as reported by Pascu,[6] leads back to 2,3-diacetoxy-4-benzoyloxybenzoic acid, mp 162–164°, identified by infrared spectra and mixture melting point.

Decarboxylation of 2,3-Dihydroxy-4-benzoyloxybenzoic Acid (**5**).—**5** was decarboxylated when heated at 255° for 5 min. The crude product was dissolved in methanol and an excess of an ether solution of diazomethane added. After 2 days the solvents were removed under reduced pressure and the residual oil, which could not be crystallized, was subjected to vapor phase chromatography on an F & M Model 402 apparatus using a 1.2-m 4% SE-30 on an Aeropack-30 column at 160° which had previously been demonstrated to be capable of separating authentic samples of 1-benzoxy-2,6-dimethoxybenzene[12] and 1-benzoxy-2,3-dimethoxybenzene.[12] The oil was shown (peak-matching technique) to be free of 1-benzoxy-2,6-dimethoxybenzene and to contain a considerable quantity of 1-benzoxy-2,3-dimethoxybenzene.

2,3-Dimethoxy-4-hydroxybenzoic Acid (**7**).—4-Benzoyloxymethyl ester **6**, mp 79–81° (lit.[6] mp 79–80°), and hydroxy acid **7**, mp 154–156° (lit.[6] 154–155°), were prepared essentially as described by Pascu.[6] We have confirmed Pascu's observations concerning the elemental analysis for both benzoate and hydroxy acid and the failure of the hydroxy acid to give a color with ferric chloride solution. Hydroxy acid **7** is not easily decarboxylated and on heating either sublimes or undergoes deep-seated decomposition.

An authentic sample of 3,4-dimethoxy-2-hydroxybenzoic acid, mp 170–172°, prepared[13] for comparison, gave a strong

(9) R. J. Highet and P. F. Highet, *J. Org. Chem.*, **30**, 902 (1965).

(10) G. W. Kirby and L. Ogunkoya, *J. Chem. Soc.*, 6914 (1965).

(11) Analyses were by Janssen Pharmaceutica Research Laboratories, Beerse, Belgium, or by Galbraith Laboratories, Knoxville, Tenn. The ultraviolet absorption spectra were measured in 95% ethanol using 1-cm quartz cells in a Cary Model 14 spectrometer. All nmr measurements are in reference to tetramethylsilane as an internal standard and unless otherwise indicated were made with a Varian A-60 spectrometer.

(12) J. Hertzig and J. Pollak, *Monatsh.*, **25**, 519 (1904).

(13) F. Mauthner, *J. Prakt. Chem.*, [2] **89**, 304 (1914); *cf.*, E. Späth and F. Boschau, *Monatsh.*, **62**, 141 (1933).

purple color with ferric chloride and was shown by mmp 133–138° and infrared spectrum to be different from 7.[14]

Methyl 2,3-Dimethoxy-4-hydroxybenzoate (8).—A slow stream of hydrogen chloride was passed through a solution of 9.9 g of hydroxy acid 7 in 30 ml of methanol for about 1 hr. The solution was allowed to stand overnight at room temperature and concentrated under vacuum. The residual colorless oil solidified on standing at room temperature. The ester was recrystallized from chloroform–petroleum ether (bp 60–90°) as colorless aggregates: mp 86–88°; yield 10 g (95%).

Anal. Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.75; H, 5.57.

The nuclear magnetic resonance spectrum of 8 in dimethyl sulfoxide was compared with that of the sodium salt in the same solvent following the directions of Highet and Highet.[9] The two aromatic protons (AB quartet) in basic solution showed an upfield shift of 0.73 and 0.30 ppm. From the data obtained by Highet and Highet for simple *p*-carbonyl phenols these observations appear to correspond well with one *ortho* (lit.[9] 0.60–0.84 ppm) and one *meta* proton (lit.[10] 0.22–0.47 ppm).

Methyl 2,3-Dimethyl-4-benzyloxybenzoate (9).—A mixture of 10.6 g of hydroxy ester 8, 8.55 g of benzyl bromide, 0.5 g of potassium iodide, and 5 g of anhydrous potassium carbonate in 250 ml of dry acetone was stirred and refluxed for 12 hr. The solids were removed by filtration and washed with acetone. The combined filtrates were concentrated under vacuum and benzene was added to the residual oil to precipitate dissolved salts. Removal of the remaining salts by filtration, followed by concentration of the filtrate and distillation of the residue, afforded 13.8 g (92%) of pale yellow oil, bp 175–180° (0.3 mm).

Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.53; H, 6.00. Found: C, 67.07; H, 6.00.

2,3-Dimethoxy-4-benzyloxybenzyl Alcohol (10).—A solution of 12.01 g of ester 9 in 50 ml of anhydrous ether was added dropwise to a stirred suspension containing 3.04 g (excess) of lithium aluminum hydride in 80 ml of dry ether. The mixture was refluxed for 8 hr, then decomposed with ethyl acetate and worked up in the usual way. The resulting orange oil was dissolved in 20 ml of carbon tetrachloride and passed through a neutral alumina column (10 × 3 cm) followed by elution with 150 ml of carbon tetrachloride. Evaporation of the solvent, finally at 100° under reduced pressure, yielded 10.4 g (95%) of a pale yellow viscous oil of analytical purity. Attempts to distil the oil at 0.3 mm resulted in extensive decomposition.

Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 69.99; H, 6.46.

N-(2',3'-Dimethoxy-4'-hydroxybenzyl)-6,7-dimethoxy-1-carboxaldoximinoisoquinolinium Bromide (12).—A solution of 2.74 g of benzyl alcohol 10 in 20 ml of methylene chloride was maintained at 0° protected from moisture and mechanically stirred while a slow stream of hydrogen bromide (dried by passage through concentrated sulfuric acid at 0°) was passed through for 10 min. After an additional 15 min most of the excess hydrogen bromide was entrained by passing dry nitrogen through the solution. Anhydrous magnesium sulfate (5 g) was added and the mixture stirred an additional 30 min under a nitrogen atmosphere. The magnesium sulfate was removed by filtration and washed with methylene chloride as rapidly as possible to avoid contact with the moisture of the air. The combined filtrates were evaporated *in vacuo* in a rotary evaporator at 20–25° and the resulting light brown viscous oil was maintained at 0° for 1 hr at 0.1-mm pressure and finally dry nitrogen was passed through until the oily product reached constant weight (3.4–3.8 g). The crude bromide obtained in this way is unstable and decomposes on standing for a few hours at room temperature. It appears to be destroyed if the temperature reaches as high as 35–40° during the evaporation procedure or if the reaction with hydrogen bromide is allowed to continue too long.

Nmr observations on the crude oil showed it to have undergone cleavage of the benzyloxy group affording an impure sample of 2,3-dimethoxy-4-hydroxybenzyl bromide (11). Attempts to prepare a bromide by the use of phosphorus tribromide instead of hydrogen bromide failed.

The crude bromide described above was dissolved with shaking in a warm solution of 2.82 g (excess) of 6,7-dimethoxyisoquinoline-1-carboxaldoxime[6] in 29 ml of pure anhydrous dimethylformamide[15] and the mixture allowed to stand for 7 days at room temperature in a well-stoppered flask. If a precipitate formed it was collected and washed with a few drops of dimethylformamide. The crystals were identified as the hydrobromide (mp 190–192°) of 6,7-dimethoxyisoquinoline-1-carboxaldoxime identified by comparison with an authentic sample.

The filtrate was mixed with 200 ml of anhydrous ether and 200 ml of ethyl acetate and allowed to stand for 6 hr at −15°. The solvents were then decanted and the viscous green residue was dissolved in 10 ml of methanol and precipitated by the addition of a mixture containing acetone, ether, and ethyl acetate in a ratio 40:20:10. The crude yellow crystals were recrystallized from methanol affording 1.2–1.3 g (25–27%) of very pale yellow aggregates, mp 209–211°.

Anal. Calcd for $C_{21}H_{23}BrN_2O_6$: C, 52.61; H, 4.83; Br, 16.67; N, 5.84. Found: C, 52.81; H, 4.79; Br, 16.35; N, 5.67.

11-Hydroxy-2,3,9,10-tetramethoxybenzo[*a*]acridizinium Bromide (13).—A solution of 1.19 g of quaternary salt 12 in 8 ml of 48% hydrobromic acid was heated on a steam bath for 30 min. The reaction mixture turned deep orange and yellow crystals usually formed. Methanol (16 ml) was added and the product allowed to crystallize. The product was recrystallized from methanol as orange-yellow needles: mp 246–248° dec; λ_{max} 220 mμ (log ε 4.05), 240 sh (4.12), 244 (4.13), 275 sh (4.12), 305 (4.34), 312 sh (4.33), 337 (4.08), 367 sh (3.71), 415 sh (3.69), 438 (3.78). The crystals turned dark within a few days.

Anal. Calcd for $C_{21}H_{20}BrNO_5 \cdot 1.5\ H_2O$: C, 53.30; H, 4.89; N, 2.96. Found: C, 53.64, 53.67; H, 4.70, 4.54; N, 2.89, 2.96.

The **perchlorate** was obtained as a very insoluble yellow powder which was purified simply by refluxing it in methanol for several minutes: mp 323–324° dec.

Anal. Calcd for $C_{21}H_{20}ClNO_9 \cdot 1H_2O$: C, 52.13; H, 4.58; N, 2.89. Found: C, 52.55; H, 4.31; N, 2.86.

The **picrate** was likewise very insoluble and was purified in the same way affording orange crystals, mp 225–257° dec.

Anal. Calcd for $C_{27}H_{22}N_4O_{12}$: C, 54.54; H, 3.73; N, 9.42. Found: C, 54.55; H, 3.65; N, 9.42.

11-Hydroxy-2,3,9,10-tetramethoxy-5,6,13,13a-tetrahydro-8H-dibenzo[*a*,*g*]quinolizine (1).—A suspension of 500 mg of the benzacridizinium compound (13) and 200 mg of platinum oxide catalyst in 150 ml of methanol was hydrogenated at atmospheric pressure and room temperature. After 5 hours, the theoretical quantity of hydrogen had been absorbed and the reaction was stopped. The catalyst was removed by filtration and the solution was evaporated to dryness. The crude hydrogenation product was suspended in 15 ml of water, the mixture was brought to pH 8.0–8.5 by the addition of 2 *N* sodium carbonate solution, and the base was extracted with methylene chloride. The dark red organic solution was treated with Norit, filtered through Supercel, and finally evaporated to dryness. The pale orange crystals were twice recrystallized from methanol affording very pale yellow aggregates: rectangular prisms; mp 192–193° dec; λ_{max} 224 mμ sh (log ε 3.96), 273 sh (3.36), 283 (3.55), 292 sh (3.38); nmr ($CDCl_3$) τ 6.17, 6.14 (each s, 3, CH_3), 6.11 (s, 6, two CH_3), 4.57 (s, 1, OH), 3.53, 3.36, 3.25 (each s, 1, aromatic H).

Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.90; H, 6.78; N, 3.77; OCH_3, 33.42. Found: C, 68.05, 67.67; H, 6.79, 6.82; N, 3.68, 3.60; OCH_3, 33.21, 33.41.

When the nmr of the base 1 was determined in dimethyl sulfoxide-d_6 and compared with the nmr of the sodium salt of the anion,[9] one aromatic proton signal was shifted upfield by only 0.22 ppm while the other two proton signals were relatively unaffected (<0.05 ppm). While this shift is lower than that reported[9] for aromatic hydrogens *ortho* to a hydroxyl group (0.42–0.59) it is not unlikely that the result could be rationalized by a study of models more closely related to 1.

(14) It was felt important to make this distinction between 3,4-dimethoxy-2-hydroxybenzoic acid and 2,3-dimethoxy-4-hydroxybenzoic acid (7) since the experiment involving the decarboxylation of the intermediate 2,3-dihydroxy-4-benzoyloxybenzoic acid (5) did not eliminate the possibility that the correct structure of the intermediate was 3,4-dihydroxy-2-benzoxybenzoic acid.

(15) The dimethylformamide was purified as recommended in Houben-Weyl, "Methoden der organischen Chemie," Vol. I, Part 2, George Thieme, Stuttgart, Germany, 1959, p 831. Probably owing to the great sensitivity of the 2,3-dimethoxy-4-hydroxybenzyl bromide to moisture, no quaternary salt was formed when unpurified commercial dimethylformamide was used, a large part of the 6,7-dimethoxyisoquinoline-1-aldoxime being recovered as the hydrobromide.

When base 1 was dissolved in dimethyl sulfoxide-d_6 and a solution of deuterium chloride in deuterium oxide added, the resulting salt solution displayed signals for the individual aromatic protons at τ 3.28, 3.16, and 2.98. After the mixture had been heated for 24 hr at 100° only the aromatic proton signal at τ 3.28 had disappeared.

The **hydrobromide** crystallized from methanol as colorless needles: mp 258–260° dec; $\lambda_{max}^{95\% EtOH}$ 224 mμ sh (log ε 3.91), 273 sh (3.34), 282 (3.53), 288 sh (3.51), 290 sh (3.42).

Anal. Calcd for $C_{21}H_{28}BrNO_5$: C, 55.78; H, 5.79; N, 3.09; OCH_3, 27.50. Found: C, 55.66; H, 5.80; N, 3.03; OCH_3, 27.41.

Comparison of 11-Hydroxy-2,3,9,10-tetramethoxy-5,6,13,13a-tetrahydro-8H-dibenzo[a,g]quinolizine (1) with Stepharotine.—About 1 mg of stepharotine hydrobromide was dissolved in water and the base liberated by addition of ammonia solution. The mixture was evaporated to dryness under reduced pressure. The residue was extracted with methylene chloride, filtered, and concentrated under reduced pressure, and the residue taken up in carbon tetrachloride.

The infrared spectrum of the resulting solution was determined using a 2-μl microcell with a Perkin-Elmer Model 21 spectrophotometer. Our hydroxy base (1) measured in the same way showed significant differences, particularly in the 8–11-μ region. Similar differences were reported to us by Dr. Kozuka who kindly compared our hydroxy base (1) with stepharotine, using chloroform as the solvent and making the infrared measurements with a Hitachi instrument.

2,3,9,10,11-Pentamethoxy-5,6,13,13a-tetrahydro-8H-dibenzo-[a,g]quinolizine (2).—To a solution of 300 mg of hydroxy base 1 in 50 ml of acetone, 1.6 g (excess) of diazomethane in 150 ml of ether was added followed by 20 ml of methanol. After 12 hr at 0° the mixture was allowed to stand 48 hr at room temperature before removal of the solvents and excess diazomethane under reduced pressure. The residue was dissolved in 50 ml of methylene chloride, then chromatographed on neutral alumina (8 × 1 cm column), and eluted with 75 ml of the same solvent. The yellow oil obtained by evaporation was crystallized from methylene chloride–ether affording 200 mg (64%) of almost colorless rectangular needles, mp 138–140° (lit.[3] mp 148–149°). In our hands a sample of the pentamethoxy compound (2) prepared by a method essentially that of Tomita, *et al.*, also melted at 138–140°. Samples of 2 prepared by the methylation of the hydroxy base and by the method of Tomita, *et al.*,[3] were found identical by means of infrared spectra and the mixture melting point: $\lambda_{max}^{75\% EtOH}$ 224 sh (log ε 3.97), 275 sh (3.34), 283 (3.48), 286 sh (3.44), 293 sh (3.30); nmr ($CDCl_3$) τ 6.20, 6.14, 6.10 (each s, 3, CH_3), 6.16 (s, 6, two CH_3), 3.52, 3.39, 3.26 (each s, 1, aromatic H).

Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.47; H, 7.11; N, 3.62.

Registry No.—**1**, 19598-17-5; **1** HBr, 19598-18-6; **2**, 7668-86-2; **5**, 19587-70-3; **8**, 19587-71-4; **9**, 19587-72-5; **10**, 19587-73-6; **12**, 19613-63-9; **13**, 19587-74-7; **14**, 19587-75-8; **15**, 19587-76-9.

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The Resolution and Absolute Configuration of the Racemic Isomer of Anaferine

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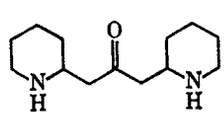
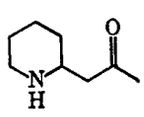
The absolute configuration of the isomers of the alkaloid anaferine, 1,3-bis(2-piperidyl)-2-propanone, was established by ORD analysis of the hydrochloride and the base obtained from the resolved dimandelates and of the isomers of pipecolic acid derived from the hydrochlorides. L-(+)-1,3-bis(2-piperidyl)-2-propanone is (*S,S*)-(+)-1,3-bis(2-piperidyl)-2-propanone and D-(−)-1,3-bis(2-piperidyl)-2-propanone is (*R,R*)-(−)-1,3-bis-(2-piperidyl)-2-propanone.

Anaferine (1) [1,3-bis(2-piperidyl)-2-propanone] was reported for the first time as a naturally occurring compound by Rother, *et al.*, in 1962.[1] This compound was originally obtained by Anet, *et al.*,[2] in their attempted synthesis of sparteine by condensation of 5-aminopentanal with acetonedicarboxylic acid at pH 11. It has also been synthesized by Schöpf, *et al.*,[3] by condensation of Δ^1-piperideine and acetonedicarboxylic acid at pH 11.5. Later it was prepared in this laboratory[4] in admixture with hygrine, cuscohygrine, anahygrine, and isopelletierine (2) from Δ^1-piperideine, 2-hydroxy-1-methylpyrrolidine, and acetonedicarboxylic acid at pH 12.

Three stereoisomers are possible: (+)-, (−)-, and *meso*-1,3-(2-piperidyl)-2-propanones. Schöpf, *et al.*,[3] separated *meso*- and DL-1,3-bis(2-piperidyl)-2-propanones as the hydrobromides and picrates. Anaferine isolated from *Withania somnifera* corresponds to the *meso* isomer.[5]



1



2

We have separated *meso*-1,3-bis(2-piperidyl)-2-propanone as the L-(+)- and D-(−)-dimandelate, (+)-1,3-bis(2-piperidyl)-2-propanone as the L-(+)-dimandelate, and (−)-1,3-bis(2-piperidyl)-2-propanone as the D-(−)-dimandelate. Using L-(+)-mandelic acid to resolve the isomeric mixture, *meso*-1,3-bis(2-piperidyl-2-propanone L-(+)-dimandelate and (+)-1,3-bis(2-piperidyl)-2-propanone L-(+)-dimandelate

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(5) A. E. Schwarting, J. M. Bobbitt, A. Rother, C. K. Atal, K. L. Khanna, J. D. Leary, and W. G. Walter, *ibid.*, **26**, 258 (1963).