Total Synthesis of Petaline[1]

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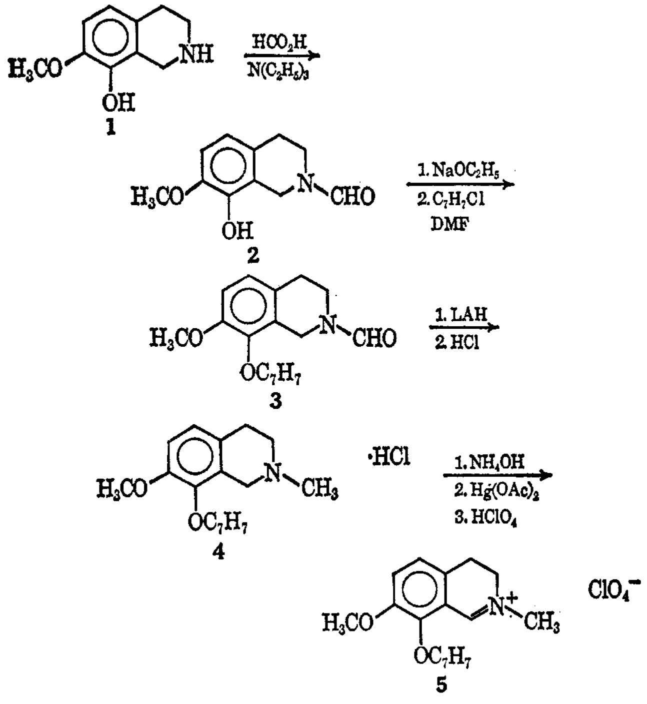
A total synthesis of petaline is described.

The quaternary benzylisoquinoline alkaloid petaline had attracted our attention because of its 7,8-oxygenation pattern which is unusual for benzylisoquinoline alkaloids. The alkaloid in the form of its chloride or reineckate was isolated[2] from extracts made from the fresh tuberous roots of *Leontice leontopetalum* Linn., a plant which grows wild in Lebanon. The extracts are used there as a folk remedy for grand mal epilepsy. The structure of petaline (**12a**) was elucidated by McCorkindale and coworkers[3] and its absolute configuration (*R*) was recently established by Craig and coworkers[4] using ORD techniques.

The total synthesis of petaline iodide (**12a**) has been achieved by the sequence of reactions in Schemes I and II.

SCHEME I



Formylation of the readily available 7-methoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline **1**[5,6] with a mixture of formic acid and triethylamine[7] gave the crystalline N-formyl derivative **2**, the sodium salt of which was benzylated with benzyl chloride in dimethylformamide. The crude O-benzyl derivative **3**, upon reduction with lithium aluminum hydride in tetrahydrofuran, afforded 8-benzyloxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, characterized as the crystalline hydrochloride **4**. Mercuric acetate dehydrogenation of the free base of **4** in 10% aqueous acetic acid at 75° led to the 3,4-dihydroisoquinolinium salt **5**, isolated as the crystalline perchlorate. The subsequent Grignard reaction was carried out by adding the solid perchlorate **5** in small portions to an excess of *p*-methoxybenzylmagnesium chloride[8] in ether. The resulting 1-benzyltetrahydroisoquinoline was isolated in the form of its hydrochloride **6** and hydrogenated in glacial acetic acid over palladium on carbon to give the debenzylated product **7a**. For its characterization the maleate **7b** was prepared. The crude free base **7a** yielded upon methylation with methyl iodide in methanol *rac*-petaline iodide, which after crystallization from acetone was isolated as hemiacetonate, mp 134–138°. The acetone content was determined spectroscopically by nmr (methyl group at 2.17 ppm, integrating for three protons) and ir (carbonyl stretching vibration at 1710 cm^{-1}) spectra and by glpc (calcd 5.99%, found 4.7%). All of the spectroscopical data (compare Experimental Section) were in accord with structure **8a**. In the low resolution mass spectrum the base peak appears at *m/e* 327 which can be assigned to a charged fragment of structure **9** which is formed formally by Hofmann degradation. The *rac*-petaline iodide was converted into *rac*-petaline reineckate (**8b**), a pink amorphous compound, mp 178–181° dec, the infrared and ultraviolet spectra of which were superimposable with those of authentic optically active material.[9] Further proof that the synthetic product represents *rac*-petaline iodide (**8a**) was provided by Hofmann degradation to petaline methine **9** on a column of Amberlite anion-exchange resin IRA-400 (OH).[3] The crystalline product obtained showed mp 119–120° and it was identical in all respects with authentic material.[9] The fragmentation pattern of the low resolution mass spectrum was very similar to that of petaline iodide; the molecular ion peak appears at *m/e* 327. The *trans*-stilbene configuration was ascertained by spectroscopic data: the ir spectrum ($CHCl_3$) showed bands at 1610 and 973 cm^{-1} and the nmr spectrum ($CDCl_3$) exhibited an AB pattern at 7.07 and 7.37 ppm (J = 16.5 cps) with integration for two protons.

For the synthesis of petaline the free base **7a** was resolved into its enantiomers by use of dibenzoyl-*d*-

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(1) Presented in part at the Natural Products Symposium in Kingston, Jamaica, Jan 1966, by A. B. and at the First International Congress of Heterocyclic Chemistry, Albuquerque, N. M., June 1967, by G. G., Abstracts, p 101. The synthesis of *rac*-petaline iodide was subject of a short communication: G. Grethe, M. Uskoković and A. Brossi, *Tetrahedron Lett.*, 1599, (1966).

(2) J. McShefferty, P. F. Nelson, J. L. Paterson, J. B. Stenlake, and J. P. Todd, *J. Pharm. Pharmacol.*, **8**, 1117 (1956).

(3) N. J. McCorkindale, D. S. Magrill, M. Martin-Smith, S. J. Smith, and J. B. Stenlake, *Tetrahedron Lett.*, 3841 (1964).

(4) J. C. Craig, M. Martin-Smith, S. K. Roy, and J. B. Stenlake, *Tetrahedron*, **22**, 1335 (1966).

(5) J. M. Bobbitt, J. McNew Kiely, K. L. Khanna, and R. Ebermann, *J. Org. Chem.*, **30**, 2247 (1965).

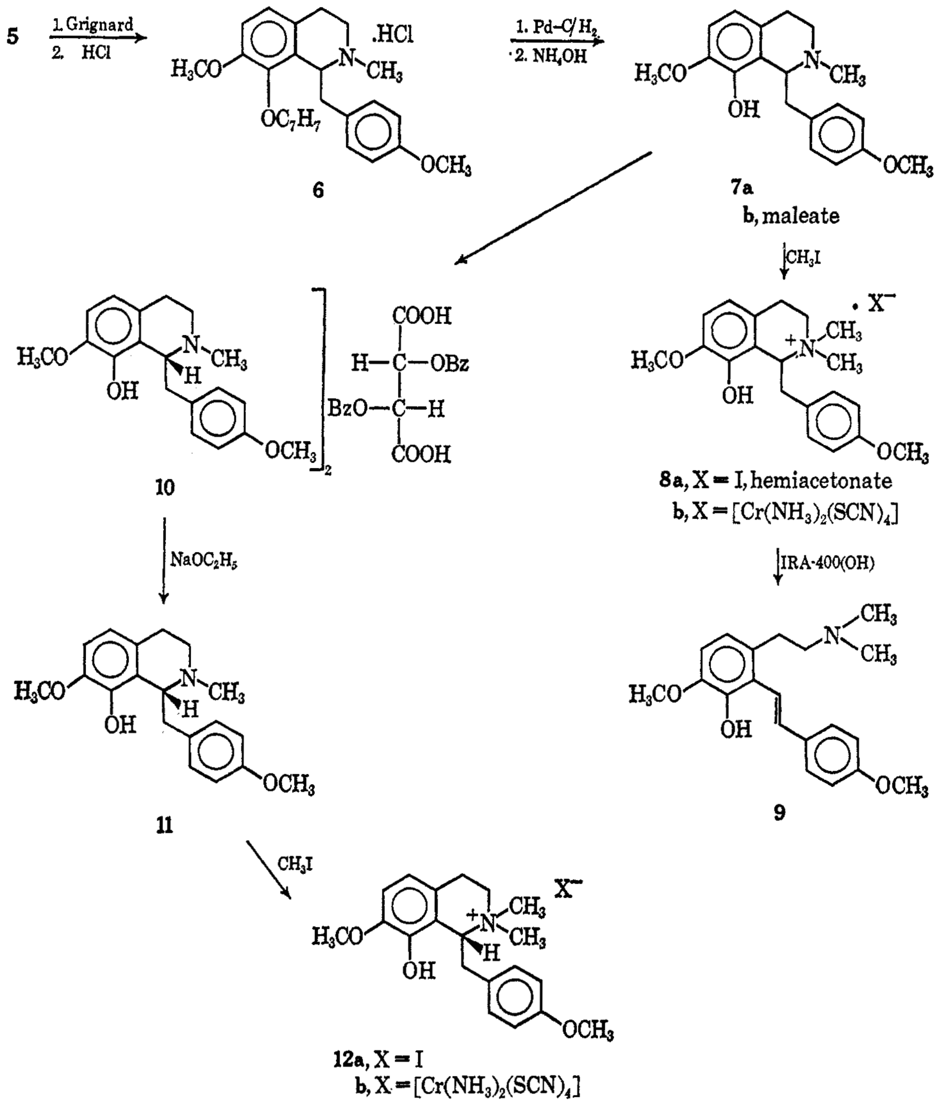
(6) G. Grethe, V. Toome, H. L. Lee, M. Uskoković, and A. Brossi, *ibid.*, **33**, 504 (1968).

(7) S. Durand, X. Lusinchi, and R. C. Moreau, *Bull. Soc. Chim. Fr.*, 270 (1961).

(8) R. C. Elderfield and V. B. Meyer, *J. Amer. Chem. Soc.*, **76**, 1886 (1954).

(9) We are grateful to Professor McCorkindale for providing us with authentic samples of petaline reineckate and petaline methine.

SCHEME II



tartaric acid. The desired diastereoisomer **10** was obtained optically pure after repeated crystallization from methanol: mp 191-192°, $[\alpha]^{24.4}D$ −62.8° (*c* 0.258, MeOH). The absolute configuration was established by ORD measurements. The ORD curve of **10** (Figure 1) showed three negative Cotton effects at 218, 242, and 293 mμ. This according to Craig and coworkers[4] indicated that **10** possesses the *R* configuration at C-1. The small distortion of the curve in the 280–290-mμ region may be attributed to superposition of the ORD curve of the tertiary amine with the one of dibenzoyl-*d*-tartaric acid which showed a strong negative Cotton effect at 241 mμ.

The dibenzoyl tartrate **10** was carefully converted into the free base **11** by treatment with 2 equiv of sodium ethoxide. The yellow oil thus obtained, $[\alpha]^{24.9}D$ −32.2° (*c* 0.165, CHCl$_3$), also exhibited in its ORD curve three negative Cotton effects at 216, 244, and 292 mμ (Figure 2). An ethereal solution of **11**, upon treatment with excess methyl iodide, gave the desired petaline iodide as a yellow, amorphous compound, $[\alpha]^{23}D$ −4.4° (*c* 0.455, 95% ethanol). The melting ranges of synthetic and natural petaline iodide were identical, 127–131° *vs.* 126–130°, and a mixture melting point showed no depression.[10] Identity was also confirmed by thin layer chromatography on silica gel G with methanol–chloroform (4:1) as the mobile phase. In this system both compounds have R_f 0.64.[10]

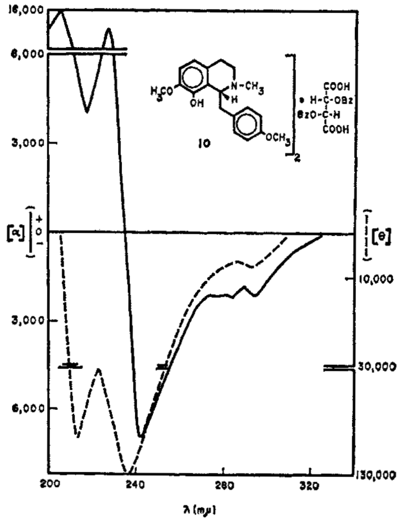


Figure 1.—ORD (—) and CD (---) curve of **10** (*c* 0.0848, CH$_3$OH).

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[10] J. C. Craig, School of Pharmacy, Department of Pharmaceutical Chemistry, University of California, San Francisco Medical Center, San Francisco, Calif., personal communication, 1967. We are thankful to Professor Craig for checking the identity of synthetic with natural petaline iodide.

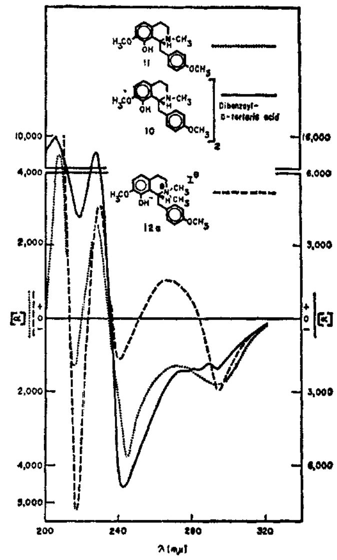

Figure 2.—ORD curves of **11** (···) (*c* 0.0464, ethanol), **10** (—) (*c* 0.0848, methanol), and **12a** (---) (*c* 0.455, 95% ethanol).

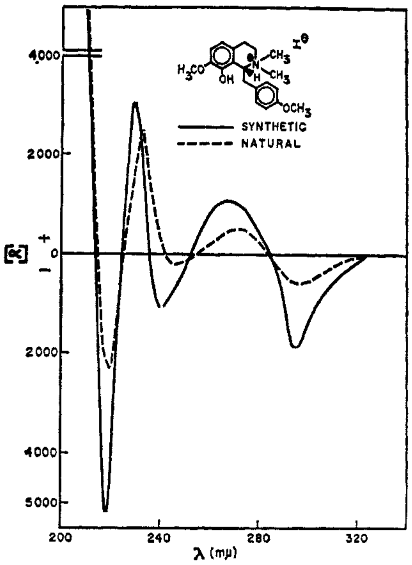

Figure 3.—ORD curves of synthetic (—) and natural (---) petaline iodide in 95% ethanol.

Furthermore, the ORD spectrum of **12a** was in good agreement with the published one[4] (Figure 3). The spectrum again showed three negative Cotton effects in the 200–300-mμ region. A comparison of the ORD curves of **10**, **11**, and **12a** (Figure 2) confirmed the findings of Craig and coworkers[4] that the absolute configuration at C-1 of 1-benzyl-1,2,3,4-tetrahydroisoquinolines can be deduced from the ORD curves of either the free base, its salt, or its methiodide.

Optically active petaline iodide finally was converted into the reineckate **12b**, a pink, amorphous compound. Its infrared spectrum was superimposable with that of natural material.[9]

Experimental Section[11]

2-Formyl,1,2,3,4-tetrahydro-7-methoxy-8-isoquinolinol (**2**).—To a mixture of formic acid and triethylamine prepared by the dropwise addition of 145 ml (3.84 mol) of formic acid (98–100%) to 111 ml (0.8 mol) of ice-cold triethylamine was added in small portions 66.3 g (0.375 mol) of **1**. After complete addition, the mixture was refluxed for 18 hr. Upon cooling to room temperature a crystalline precipitate was obtained, collected by filtration, and washed with acetone and subsequently with ether to give 68.3 g (89%) of the N-formyl derivative **2**, mp 174–177°. A sample after recrystallization from methanol afforded analytically pure **2**: mp 177–179°; $\nu_{max}^{CHCl_3}$ 3545 (OH), 1670 (C=O), and 1285 and 1240 cm^{-1} (OCH_3 and OH); $\lambda_{max}^{isopropyl\ alcohol}$ 230 mμ (ε 6800) (sh), 280 (2300); $\lambda_{max}^{0.1\ N\ KOH}$ 246 mμ (ε 7200), 292 (4500); nmr ($CDCl_3$),[12] δ 2.82 (2 H, rough triplet, *J* = 6 cps, CH_2-4), 3.63 and 3.78 (2 H, 2 t, *J* = 6 cps, CH_2-3), 3.88 (3 H, s, OCH_3), 4.55 and 4.68 (2 H, 2 s, CH_2-1), 5.72 (1 H, exchange, s, OH), 6.70 (2 H, barely resolved AB pattern, CH-5 and CH-6), 8.22 and 8.28 (1 H, 2 s, CHO).

Anal. Calcd for $C_{11}H_{13}NO_3$ (207.23): C, 63.76; H, 6.32; N, 6.76. Found: C, 63.93; H, 6.49; N, 6.61.

8-Benzyloxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (**4**).—To a solution of 68.3 g (0.33 mol) of **2** in 2.5 l. of methanol was added 17.8 g (0.33 mol) of sodium methoxide. The mixture was kept at room temperature for 1 hr followed by removal of the solvent under reduced pressure. In order to assure dryness of the solid sodium salt *ca.* 500 ml of benzene was added to the residue and then removed under reduced pressure. This procedure was repeated twice. The residue then was suspended in 1.8 l. of freshly distilled dimethylformamide, 37.9 ml of benzyl chloride was added, and the mixture was stirred at 100° for 70 hr. After removing the solvent at 45° under a pressure of 1 mm, 500 ml of benzene was added to the residue and the insoluble parts were removed by filtration. The filtrate was evaporated to dryness under vacuum to give 104 g of crude oily **3**. This was dissolved in 3.2 l. of anhydrous tetrahydrofuran, and to the cooled solution was added cautiously 26.3 g of lithium aluminum hydride in small portions. After complete addition the stirred mixture was refluxed overnight in a nitrogen atmosphere. Stirring was continued while the mixture was cooled in an ice bath and a saturated aqueous solution of sodium sulfate was added cautiously until the hydrogen evolution ceased. The mixture then was filtered, and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in 200 ml of methanol and excess isopropyl alcoholic hydrogen chloride was added. Upon addition of ether to the solution a crystalline precipitate was formed which when filtered gave 56 g (53%) of **4**, mp 187–189°. An analytical sample after recrystallization from methanol showed the following properties: mp 191.5–192.5°; $\nu_{max}^{CHCl_3}$ 2350 (broad, *t*-amine salt), 1500 (phenyl), and 1285 and 1245 cm^{-1} (OCH_3 and OC_7H_7); $\lambda_{max}^{isopropyl\ alcohol}$ 230 mμ (ε 8210) (sh), 282 (2220); nmr ($CDCl_3$), δ 2.71 (3 H, d, *J* = 5 cps, ^+N–CH_3), 2.8–3.7 (4 H, m, CH_2-3 and CH_2-4), 3.87 (3 H, s, OCH_3), 3.70 and 4.37 (2 H, AB part of ABX pattern, J_{AB} = 15 cps, $J_{AX,BX}$ = 3 cps, CH_2-1), 5.01 and 5.12 (2 H, AB pattern, *J* = 11 cps, O–CH_2), 6.88 (2 H, s, CH-5 and CH-6), 7.35 (5 H, s, phenyl), 12.68 (1 H, b, ^+NH).

Anal. Calcd for $C_{18}H_{21}NO_2 \cdot HCl$ (319.84): C, 67.61; H, 6.93; N, 4.38. Found: C, 67.37; H, 7.23; N, 4.36.

8-Benzyloxy-7-methoxy-2-methyl-3,4-dihydroisoquinolinium Perchlorate (**5**).—To a methanolic solution of 13.4 g (0.42 mol) of **4** was added 95 ml of ethanol containing 2.84 g (0.42 mol) of sodium ethoxide. The solvent was removed under reduced pressure and the residue was treated with methylene chloride. The mixture was filtered and the filtrate was evaporated to dryness under reduced pressure. The oily residue was dissolved in 240 ml of 10% acetic acid, a solution of 53.5 g (0.168 mol) of mercuric acetate in 240 ml of 10% acetic acid was added, and the

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[11] Melting points were taken in capillaries with a Thomas–Hoover melting point apparatus and are uncorrected. Infrared spectra were determined with a Beckman infrared spectrophotometer, Model IR-9. The uv spectra were recorded on a Cary Recording spectrophotometer, Model 14 M. Rotatory dispersion curves were measured at 23° with a Durrum-Jasco spectrophotometer, Model 5, using 1-cm, 0.1-cm, or 0.1-mm cells. Specific rotations are given for the highest and lowest wavelength measured, for intersections, and for peaks and troughs. Circular dichroism curves were measured on the same instrument and they are recorded in molecular ellipticity units [Θ]. Optical rotations were measured on a Perkin-Elmer polarimeter, Model 141. Nuclear magnetic resonance spectra were obtained on a Varian Associates spectrophotometer, Model A-60 or HA-100, and chemical shifts are reported in δ using tetramethylsilane as internal reference (δ 0). The following abbreviations are used in connection with the nmr data: (s) singlet, (d) doublet, (t) triplet, (q) quartet, (b) broad featureless peak, (cp) complex band pattern, (m) multiplet. The mass spectra were taken with a CEC 21-110 mass spectrometer at 70 eV using a direct insertion probe.

[12] The nmr spectrum indicates that in solution **2** exists in two isomeric forms in about a 1:1 ratio. Some of the corresponding signals overlap each other and the integration is therefore given of the total protons of each group.

mixture was stirred in a nitrogen atmosphere at 75° for 40 hr. The precipitated mercurous acetate was removed by filtration, and hydrogen sulfide was passed into the filtrate. The black precipitate was removed by filtration, and the filtrate was concentrated under reduced pressure. The oily residue was dissolved in methanol, excess isopropyl alcoholic hydrogen chloride and acetone was added, and the mixture was kept at 5° overnight. The solution was decanted from the small amounts of precipitate formed and evaporated to dryness under reduced pressure, and the residue was dissolved in water. Upon addition of excess 60% perchloric acid an oil was precipitated which slowly crystallized on standing at room temperature. The precipitate was collected by filtration and recrystallization from methanol gave 8.3 g (52%) of **5**, mp 178–180°. For analysis a sample was recrystallized from methanol: mp 181–183°; ν_{max}^{KBr} 1665 ($C{=}^+N$), 1605, 1580 and 1500 (phenyl), and 1285 and 1258 cm^{-1} (OCH_3 and OC_7H_7); λ_{max} 239 mμ (ϵ 13,200), 301 (11,760), 379 (2700); nmr (DMSO-d_6), δ 3.07 (2 H, t, J = 8 cps, CH_2-4), 3.76 (3 H, s, ^+N–CH_3), 3.93 (3 H, s, OCH_3), $\sim$3.9 (2 H, t, J = 8 cps, partially hidden by the ^+N–CH_3 and OCH_3 signals, CH_2-3), 5.22 (2 H, s, OCH_2–C_6H_5), 7.13 and 7.47 (2 H, AB pattern, J = 8 cps, CH-5 and CH-6), 7.43 (5 H, s, phenyl).

Anal. Calcd for $C_{18}H_{20}ClNO_6$ (381.83): C, 56.62; H, 5.28; N, 3.67. Found: C, 56.87; H, 5.39; N, 3.44.

1-(4-Methoxybenzyl)-8-benzyloxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (6).—To 56.5 g (2.32 g-atoms) of magnesium turnings covered with 250 ml of anhydrous ether was added 0.5 g of iodine and 4 g of *p*-methoxybenzyl chloride.[13] The reaction started immediately. Without stirring the mixture was refluxed for 10 min and then 14.2 g of the chloride (total 0.116 mol) in 110 ml of dry ether was added over 30 min with vigorous stirring. After stirring and refluxing for an additional 40 min the mixture was allowed to settle. The clear solution was carefully decanted from the residue and filtered through a Büchner funnel (fritted disk) under slight nitrogen pressure. To the stirred filtrate was added within 15 min 10 g (26.2 mmol) of **5** under nitrogen atmosphere. With continued stirring the mixture was then refluxed for 1 hr and cooled to room temperature. After 20 ml of methanol was added cautiously the ethereal solution was decanted and treated with excess isopropyl alcoholic hydrogen chloride. Oily material precipitated which slowly crystallized to give 6.3 g of **6**, mp 170–180°. The residue was treated with chloroform, and the organic layer was washed successively with 3 *N* hydrochloric acid and water, dried, filtered, and evaporated to dryness under reduced pressure. The oily residue was dissolved in methanol, the solution was treated with isopropyl alcoholic hydrogen chloride and on addition of ether another 3.1 g of crystalline hydrochloride **6**, mp 186–192°, was obtained. The two crystalline fractions were combined and recrystallized from methanol–ether to furnish in two crops (6.2 g with mp 191–193° and 2.9 g with mp 185–190°) a total of 9.1 g (79%) of **6**. An analytical sample recrystallized from methanol–ether showed the following properties: mp 191–193°; $\nu_{max}^{CHCl_3}$ 2420 (broad, *t*-amine salt), 1613, 1580 and 1510 (phenyl), and 1285 and 1255 cm^{-1} (OCH_3 and OC_7H_7); $\lambda_{max}^{isopropyl\ alcohol}$ 229 mμ (ϵ 25,200), 278 (4560), 283–284 (4490); nmr ($CDCl_3$), δ 2.2–5.0 (5 H, cp, CH-1, CH_2-3, and CH_2-4), 3.43 (3 H, d, J = 5 cps, ^+N–CH_3), 3.74 (3 H, s, OCH_3-4), 3.96 (3 H, s, OCH_3-7), 5.08 (2 H, s, OCH_2–C_6H_5), 6.6–7.5 (6 H, cp, aromatic protons), 7.30 (5 H, s, phenyl), 12.4 (1 H, b, ^+NH).

Anal. Calcd for $C_{26}H_{29}NO_3 \cdot HCl$ (440.00): C, 70.97; H, 6.87; N, 3.18. Found: C, 70.71; H, 6.82; N, 3.17.

1-(4-Methoxybenzyl)-1,2,3,4-tetrahydro-7-methoxy-2-methyl-8-isoquinolinol Maleate (7b).—A solution of 12.8 g of **6** in 650 ml of glacial acetic acid was hydrogenated over 3 g of 10% palladium on carbon at atmospheric pressure and at an initial temperature of 70°. During the hydrogenation the mixture was allowed to cool to room temperature. After the hydrogen uptake ceased ($\sim$6 hr), the catalyst was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. The oily residue was taken up in 100 ml of water, 100 ml of chloroform was added, and the vigorously stirred suspension was treated with an excess of sodium bicarbonate. The chloroform layer was separated, and the aqueous phase was washed with three 100-ml portions of chloroform. The combined organic solution was washed with water, dried over sodium sulfate, filtered, and evaporated to dryness under reduced pressure to give 10.7 g of the free base **7a** as a brown oil. This material could be used for the next step without further purification. For characterization the maleate **7b** was prepared. To a solution of 1.72 g of the oil in ether was added a solution of 700 mg of maleic acid in 50 ml of ether. The precipitated solid material was collected by filtration and crystallized from ethanol–ether to give 2 g of **7b**, mp 152–155° with softening at 80°. After two recrystallizations from ethanol–ether analytically pure **7b** showed two melting points at 77–79 and 155°; $\nu_{max}^{CHCl_3}$ 3540 (OH), 2450 (broad, *t*-amine salt), 1710 (COOH), 1620 (COO^-), 1610, 1580 and 1510 (phenyl), and 1285 and 1255 cm^{-1} (OCH_3 and OH); $\lambda_{max}^{CH_3OH}$ 225 mμ (ϵ 26,000) (sh), 278 (4000), 284 (3800); $\lambda_{max}^{0.1\ N\ KOH}$ 250 mμ (ϵ 8000) (sh), 275 (4200) (sh), 283 (4700), 293 (4400) (sh).

Anal. Calcd for $C_{19}H_{23}NO_3 \cdot C_4H_4O_4$ (429.47): C, 64.33; H, 6.34; N, 3.26. Found: C, 64.28; H, 6.66; N, 3.46.

Racemic Petaline Iodide Hemiacetonate (8a).—A solution of 1.375 g of the crude free base **7a** and 3.5 ml of freshly distilled methyl iodide in 50 ml of methanol was refluxed overnight. The solvent was removed under reduced pressure and the oily residue was triturated with 5 ml of acetone to give 1.555 g (78%) of crystalline **8a**, mp 134–138° dec. The volume of a solution of 250 mg of this material in 250 ml of acetone was reduced to 100 ml by evaporation under reduced pressure at room temperature. The crystalline material obtained on standing was collected by filtration and dried for 50 hr at 50° under vacuum to give analytically pure **8a**: mp 134–138° dec; $\nu_{max}^{CHCl_3}$ 3530 (OH), 1710 (acetone, C=O), 1610, 1510 and 1500 (phenyl), and 1285 and 1250 cm^{-1} (OCH_3 and OH); $\lambda_{max}^{isopropyl\ alcohol}$ 223 mμ (ϵ 28,200), 279–280 (3980), 284–285 (3980); nmr ($CDCl_3$), δ 2.17 (3 H, s, acetone), 3.35 and 3.50 (3 H each, s, ^+N–CH_3), 3.77 and 3.92 (3 H each, s, OCH_3), 2.9–4.4 (4 H, cp, partially buried, CH_2-3 and CH_2-4), 5.07 (1 H, b, CH-1), 6.23 (1 H, s, OH), 6.5–7.4 (6 H, cp, aromatic protons); mass spectrum, fragments at *m/e* 327 (base peak), 206, 192, 177, 142, 121, and 58; acetone determination by glpc (calcd 5.9% w/w), found 4.7% w/w.

Anal. Calcd for $C_{20}H_{26}NO_3I \cdot {}^1/_2CH_3COCH_3$ (484.39): C, 53.31; H, 6.04; N, 2.89. Found: C, 53.47; H, 6.14; N, 2.93.

Racemic Petaline Reineckate (8b).—Treatment of an aqueous solution of **8a** with a saturated aqueous solution of ammonium reineckate afforded a pink amorphous solid which was further purified by precipitation from an aqueous solution with acetone. The racemic petaline reineckate (**8b**) thus obtained showed the following properties: mp 178–181° dec; ν_{max}^{KBr} 3500 (OH), 2080 (SCN), 1610, 1520 and 1500 (phenyl), and 1288, 1255, and 1242 cm^{-1} (OCH_3 and OH); λ_{max} (isopropyl alcohol + 10% Methyl Cellosolve) 233 mμ (ϵ 35,800), 280 (12,000), 284 (12,100), 311 (17,600).

Petaline Methine (9).—A solution of 7.5 g of racemic petaline iodide in 75 ml of 80% ethanol was applied to a column of 1000 ml of Amberlite anion exchange resin IRA-400 (OH) and left there for 15 hr. Elution with 900 ml of 80% ethanol at a rate of 3 ml/min and evaporation of the eluate under reduced pressure gave an oily residue. Trituration of the residue with 50 ml of ethanol afforded 4 g (79%) of crystalline petaline methine (**9**), mp 120–122°. An analytical sample was recrystallized twice from methanol–water and showed the following properties: mp 119–120°; $\nu_{max}^{CHCl_3}$ 3530 (OH), 1610 and 973 (C=C, *trans*-stilbene), 1605, 1580 and 1515 (phenyl), and 1285 and 1255 cm^{-1} (OCH_3 and OH); $\lambda_{max}^{isopropyl\ alcohol}$ 214 mμ (ϵ 30,500), 240 (11,900) (sh), 300 (24,900), 321 (21,000) (sh); $\lambda_{max}^{0.1\ N\ KOH}$ 251 mμ (ϵ 19,600), 290 (16,700), 357 (8200) (sh); nmr ($CDCl_3$), δ 2.32 [6 H, s, $N(CH_3)_2$], 2.75 (4 H, m, CH_2–CH_2), 3.83 and 3.88 (3 H each, s, OCH_3), 6.42 (1 H, s, OH), 6.72 (2 H, s, CH-5 and CH-6), 6.88 and 7.37 (4 H, A_2B_2 pattern, J = 9 cps, CH-2′, CH-3′, CH-5′ and CH-6′), 7.07 and 7.37 (2 H, AB pattern, J = 16.5 cps, *trans* CH=CH); mass spectrum, fragments at *m/e* 327 (molecular ion), 206, 177, 121, and 58.

Anal. Calcd for $C_{20}H_{25}NO_3$ (327.43): C, 73.37; H, 7.70; N, 4.28. Found: C, 73.36; H, 7.43; N, 4.31.

(*R*)-(−)-**1-(4-Methoxybenzyl)-1,2,3,4-tetrahydro-7-methoxy-2-methyl-8-isoquinolinol Dibenzoyl-*d*-tartrate (10).**—The oily free base **7a**, obtained from 3.7 g of **6** as previously described, was dissolved in 100 ml of ether. Addition of 3.3 g of dibenzoyl-*d*-tartaric acid in 50 ml of ether gave a solid precipitate which, recrystallized from hot methanol, afforded 1.414 g of dibenzoyl-*d*-tartrate **10**, $[\alpha]^{25}D$ −60.4° (*c* 0.262, MeOH). Several recrystallizations to constant rotation yielded analytically pure material: mp 191–192°; $[\alpha]^{24.4}D$ −62.8° (*c* 0.258, MeOH), $[\alpha]_{365}^{24.4}$ −326° (*c* 0.258, MeOH); ORD and CD curve, see Figure 1; λ_{max}^{MeOH}

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[13] J. Lee, A. Ziering, L. Berger, and S. D. Heineman, *Festschr. Emil Barrel*, 264 (1946); *Chem. Abstr.*, **41**, 6252 (1947).

227-228 mμ (ε 68,500), 278 (9500), 284 (8800) (sh); $\lambda_{\max}^{0.1\,N\ \mathrm{KOH}}$ 225 mμ (ε 67,500) (sh), 276 (11,100) (sh), 282-283 (11,800), 296 (9000) (sh); $\nu_{\max}^{\mathrm{KBr}}$ 2550 (broad, *t*-amine salt), 1720 (ester C═O), 1625 and 1615 (COO^-), 1617, 1585 and 1505 (phenyl), and 1280 cm^{-1} (broad, ester, OCH_3, and OH).

Anal. Calcd for $C_{38}H_{46}N_2O_6 \cdot C_{18}H_{14}O_8$ (985.12): C, 68.28; H, 6.14; N, 2.84. Found: C, 68.47; H, 6.08; N, 3.02.

(*R*)-(−)-**1-(4-Methoxybenzyl)-1,2,3,4-tetrahydro-7-methoxy-2-methyl-8-isoquinolinol** (**11**).—To a solution of 281.5 mg (0.285 mmol) of **10** in 200 ml of methanol was added 5.15 ml of ethanol containing 38.85 mg (0.572 mmol) of sodium ethoxide. The solvent was removed under reduced pressure and the residue was extracted with ether to give 162 mg of **11** as a yellow oil: $[\alpha]^{24.9}\mathrm{D}$ −32.2° (*c* 0.165, $CHCl_3$), $[\alpha]^{24.9}_{365}$ −326° (*c* 0.165, $CHCl_3$); for the ORD curve see Figure 2; CD (*c* 0.0464, ethanol), $[\Theta]_{300}$ 0, $[\Theta]_{278}$ −2829, $[\Theta]_{255}$ −1338, $[\Theta]_{235}$ −19,624, $[\Theta]_{230}$ −9366; $\nu_{\max}^{\mathrm{CHCl_3}}$ 3545 (OH), 1610, 1588, 1515 and 1495 (phenyl), and 1280 and 1250 cm^{-1} (OCH_3 and OH); $\lambda_{\max}^{\mathrm{CH_3OH}}$ 226 mμ (ε 21,300), 278 (3900), 284 (3600); nmr ($CDCl_3$), δ 2.31 (3 H, s, N-CH_3), 2.2-3.3 (6 H, cp, methylene protons), 3.72 and 3.81 (3 H each, s, OCH_3-4 and OCH_3-7), 4.00 (1 H, q, J = 4.5 cps, CH-1), 5.82 (1 H, b, OH), 6.55 and 6.68 (2 H, AB pattern, J = 8.5 cps, CH-5 and CH-6), 6.77 and 7.17 (4 H, A_2B_2 pattern, J = 8 cps, CH-2′, CH-3′, CH-5′ and CH-6′); mass spectrum, fragments at *m/e* 313, 312, 192 (base peak), 177.

Petaline Iodide (**12a**).—To the oily free base **11** (150 mg) in 20 ml of anhydrous ether was added within 20 min a solution of 1 ml of freshly distilled methyl iodide in 3 ml of anhydrous ether. The mixture was left at room temperature overnight, and the amorphous yellow precipitate was collected by filtration and washed thoroughly with ether to give 168 mg of **12a** melting between 107 and 116° after drying at 40° for 3 days under reduced pressure: for the optical rotatory dispersion curve see Figures 2 and 3; $[\alpha]^{23}\mathrm{D}$ −4.4° (*c* 0.455, 95% ethanol); CD (*c* 0.455, 95% ethanol), $[\Theta]_{310}$ 0, $[\Theta]_{288}$ −9108, $[\Theta]_{253}$ −528, $[\Theta]_{235}$ −21,120, $[\Theta]_{225}$ −5280, $[\Theta]_{212}$ −84,480, $[\Theta]_{205}$ 0.

Petaline Reineckate (**12b**).—To 25 ml of an aqueous solution of **12a** (140 mg) was added a saturated aqueous solution of ammonium reineckate until no more material was precipitated. The amorphous pink precipitate was collected by filtration and dried 3 days at 50° under reduced pressure to give 128 mg of **12b**, melting between 135 and 145° dec; a mixture melting point with authentic material[9] showed no depression and the infrared spectra (KBr) were superimposable. Reprecipitation from an aqueous solution with acetone afforded, after drying at room temperature for 80 hr under reduced pressure, **12b** which melted between 126 and 134°: $[\alpha]^{23}\mathrm{D}$ −1.5° (*c* 0.647, ethanol); ORD (*c* 0.647, ethanol), $[\alpha]_{320}$ −386°, $[\alpha]_{292}$ −850° (tr), $[\alpha]_{284}$ 0°, $[\alpha]_{270}$ +540° (pk), $[\alpha]_{253}$ 0°, $[\alpha]_{241}$ −540° (tr), $[\alpha]_{235}$ 0°, $[\alpha]_{228}$ +1620° (pk), $[\alpha]_{216}$ −1390° (tr), $[\alpha]_{212}$ −773°; CD (*c* 0.647, ethanol), $[\Theta]_{305}$ 0, $[\Theta]_{288}$ −7920, $[\Theta]_{268}$ 0, $[\Theta]_{235}$ −23,100, $[\Theta]_{223}$ −1320, $[\Theta]_{215}$ −42,900.

By paper chromatography (descending, pyridine-water 1:4, Whatman No. 1 paper), **12b** was identical with authentic material,[9] R_f 0.83. The spots were developed with modified Dragendorff reagent.[14]

Registry No.—**2**, 6068-43-5; **4**, 6077-99-2; **5**, 5890-46-0; **6**, 5890-47-1; **7b**, 16336-16-6; **8a**, 16350-27-9; **8b**, 15612-34-7; **9**, 2609-29-2; **10**, 16346-57-9; **11**, 16336-17-7; **12a**, 6392-37-6; **12b**, 16351-46-5.

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Synthetic Quinine Analogs. I. The Synthesis and Some Chemical Transformations of 6′-Methoxy-7-oxo-8-rubene[1]

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Sodium ethoxide-catalyzed condensation of 6-methoxyquinoline-4-carboxaldehyde with 3-quinuclidinone produces 6′-methoxy-7-oxo-8-rubene in high yield. Of the two possible geometrical isomers, only that with the ketone function *trans* to the quinoline ring is formed. Reduction of the ketone affords an allylic alcohol whose *p*-nitrobenzoate is completely isomerized to the opposite geometrical isomer in refluxing acetic acid. The ketone is not ketalized by 1,2-ethanedithiol in refluxing trifluoroacetic acid but instead undergoes a remarkable condensation reaction involving one molecule of ketone, two of 1,2-ethanedithiol, and one of trifluoroacetic acid. A by-product of the reaction results from the condensation of three molecules of 1,2-ethanedithiol with two of trifluoroacetic acid. Pyrazoline derivatives of the ketone resulting from 1,3-dipolar addition of diazomethane and condensation with hydrazine are described.

As a sequel to their brilliant degradative studies which elucidated the structure of quinine,[3] Rabe and his coworkers undertook its synthesis in the 1920's.[4] While this substance constituted a rather ambitious synthetic objective for the time, a general route to the quinine skeleton was developed by which total syntheses of dihydroquinine and dihydroquinidine were accomplished in 1931.[5] In its basic form [Claisen condensation of a β-(4-piperidyl)propionate with ethyl quininate followed by decarboxylation, bromination, and cyclization], the Rabe route formed the cornerstone of most of the subsequent synthetic work in the area. Both Rabe[6] and Prelog,[7] *et al.*, used this route extensively for the preparation of synthetic quinine analogs and, in the hands of Woodward and Doering,[8] it was utilized to effect the total synthesis of quinine itself.

Much of the more recent synthetic work on the

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[2] National Science Foundation Undergraduate Research Participant.

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