terial (vpc, SE-30, 200°). Upon distillation, a main cut, 94 g, bp 77° (15 mm), n^{20}D 1.4545, of a 91:9 isomeric mixture of **6** and **6a** (vpc, 20M, 90°) was obtained.

Cyclization of 9.—*trans*-2,6-Dimethyl-2,4-octadien-8-ol (**9**, 16 g), benzene (32 ml), and *p*-toluenesulfonic acid (0.5 g) were refluxed for 14 hr; upon neutralization and evaporation of the solvent, 13 g were obtained, n^{20}D 1.4620, showing the following composition: 23% **7** and **7a**; 53% **6**; 9% **6a**; and 15% unreacted **9**.

Cyclization of 9a.—*cis*-2,6-Dimethyl-2,4-octadien-8-ol (**9a**, 15 g) and 30% H_2SO_4 (15 ml) were vigorously agitated at room temperature (20–30°) for 22 hr. The reaction mixture, after neutralization, afforded 14 g, which showed the following composition (vpc, 20M, 90°): 1% **7** and **7a**; 39% **6**; 6% **6a**; and 54% unreacted **9a**.

***cis* and *trans*-2-(2-Methyl-2-hydroxyprop-1-yl)-4-methyltetrahydropyran (10 and 10a).**—*trans*-2,6-Dimethyl-2,4-octadien-8-ol (**9**, 100 g) was fed within 5 min, under cooling at 0–10°, into 62.5% H_2SO_4 (100 ml); the temperature was left to reach 20–25° within 5 min. The reaction product was then poured onto 30% NaOH (200 ml) under cooling (30–40°), and the top layer separated; it afforded, upon distillation, 75 g of a main cut, bp 75–80° (2 mm), n^{20}D 1.4480, of a 95:5 *cis–trans* mixture of hydroxyrosoxide (**10** and **10a**) (vpc, SE-30, 190°).

Conversion of 10 into a Mixture of Rosoxides 6 and 6a.—Hydroxyrosoxide **10** (100 g), benzene (400 ml), and concentrated H_2SO_4 (4 g) were heated under reflux for 1 hr (80–82°) while water was azeotroped off in a Dean–Stark trap. The mixture, after neutralization and distillation, afforded 70 g, n^{20}D 1.4550, consisting of 30% **7**, 2% **7a**, 64% **6**, and 4% **6a** (vpc, CW 20M, 90°); *cf.* ref 4.

***cis*-Rosoxide** [*cis*-2-(2-methyl-1-propen-1-yl)-4-methyltetrahydropyran, **6**], separated by distillation through a Nester–Faust Teflon spinning-band column, gave the following data: bp 86° (20 mm); n^{20}D 1.4535.

The nmr spectrum follows: H at C_1, d, fine splitting, δ 5.09, J = 8.5 Hz; H at C_2 and H at C_6, m, δ 3.9; H at C_6, six-peak m, composed of 3 d, with axial fixed conformation, δ 3.38, J_{gem} = 12 Hz, J' = 12 Hz, J'' = 2.5 Hz; 6 H of $(CH_3)_2C=$, 2 d, δ 1.68, and 1.65, J = 1 Hz; 3 H of CH_3CH, d, δ 0.90, J = 5 Hz.

***trans*-Rosoxide** [*trans*-2-(2-methyl-1-propen-1-yl)-4-methyltetrahydropyran, **6a**, separated by distillation through a Nester–Faust Teflon spinning-band column, gave the following data: bp 88–89° (20 mm); n^{20}D 1.4580.

The nmr spectrum follows: H at C_1, d, fine splitting, δ 5.22, J = 8 Hz; H at C_2, six-peak m, composed of 3 d, δ 4.29, J = 8 Hz, J' = 8 Hz, J'' = 4 Hz, 2 H at C_6, m, nearly equivalent protons owing to flipping of conformation of *trans* configuration, δ 3.5–3.8; 6 H of $(CH_3)_2C=$, d, δ 1.66 and 1.69, J = 1 Hz; 3 H of CH_3CH, d, δ 1.04, J = 6 Hz.

Registry No.—**1**, 23062-48-8; **2**, 23102-71-8; **3**, 23042-11-7; **3a**, 23061-96-3; **4**, 23062-49-9; *trans*-**5**, 23061-97-4; **6**, 876-17-5; **6a**, 876-18-6; **8**, 23062-00-2; **9**, 23062-01-3; **9a**, 23062-02-4; **10**, 23062-03-5; **10a**, 23062-04-6; *cis*-2,6-dimethyl-1,8-dihydroxy-2-octene, 23062-05-7; *trans*-2,6-dimethyl-1,8-dihydroxy-2-octene, 23062-07-9; *cis*-**5**, 23062-08-0.

Cherylline, a 4-Phenyl-1,2,3,4-tetrahydroisoquinoline Alkaloid

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A 4-phenyl-1,2,3,4-tetrahydroisoquinoline alkaloid, cherylline, has been isolated from *Crinum powellii*. The alkaloid has been assigned the structure **12** from spectral, degradative, and synthetic evidence. A facile synthesis of (±)-O,O-dimethyl-N-demethylcherylline (**5**) provided an intermediate capable of resolution. N-Methylation of the *S* enantiomer (**10a**) provided a product, the hydrochloride of which was identical with O,O-dimethylcherylline hydrochloride.

Isolation and separation procedures reported during the past 20 years have provided relatively few phenolic *Amaryllidaceae* alkaloids.[2] We wish to report the isolation and structure of cherylline, a new representative of this rare type of phenolic alkaloid. Cherylline,[3] which is optically active, has been isolated in *ca.* 0.004% yield from the alkali-soluble crude alkaloids of several species of *Crinum*. The nmr spectrum of cherylline in DMSO-d_6 exhibits an A_2B_2 pattern (δ 6.91 and 6.64) characteristic of a 1,4-disubstituted aromatic ring, two one-proton singlets (δ 6.49 and 6.23) indicative of two *para*-oriented protons on a second aromatic ring, and two three-proton singlets at δ 3.51 (OCH_3) and 2.24 (NCH_3) in addition to a few less well-defined signals. The ultraviolet spectrum of the compound has maxima at 285 and 280 mμ which undergo a bathochromic shift to 299 mμ upon the addition of base. The mass spectrum and elemental analysis of the alkaloid indicate a molecular weight of 285 and the empirical formula $C_{17}H_{19}NO_3$. These results are consistent with a compound containing two aromatic rings (both phenolic), N-methyl and methoxyl groups, and a C_3H_5 fragment. Structure **1** is in agreement with the spectroscopic data. Proof that the alkaloid does contain this skeleton was obtained by converting cherylline into O,O-dimethylcherylline (**1**, CH_3O instead of OH) with diazomethane. This fully methylated derivative exhibited R_f values on silica gel with several different solvent systems that were identical with those found for synthetic (±)-6,7-dimethoxy-4-(4′-methoxyphenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (**6**). The ir spectra (KBr) of the hydrochlorides of both compounds were superimposable, thus confirming their chemical identity.[4]

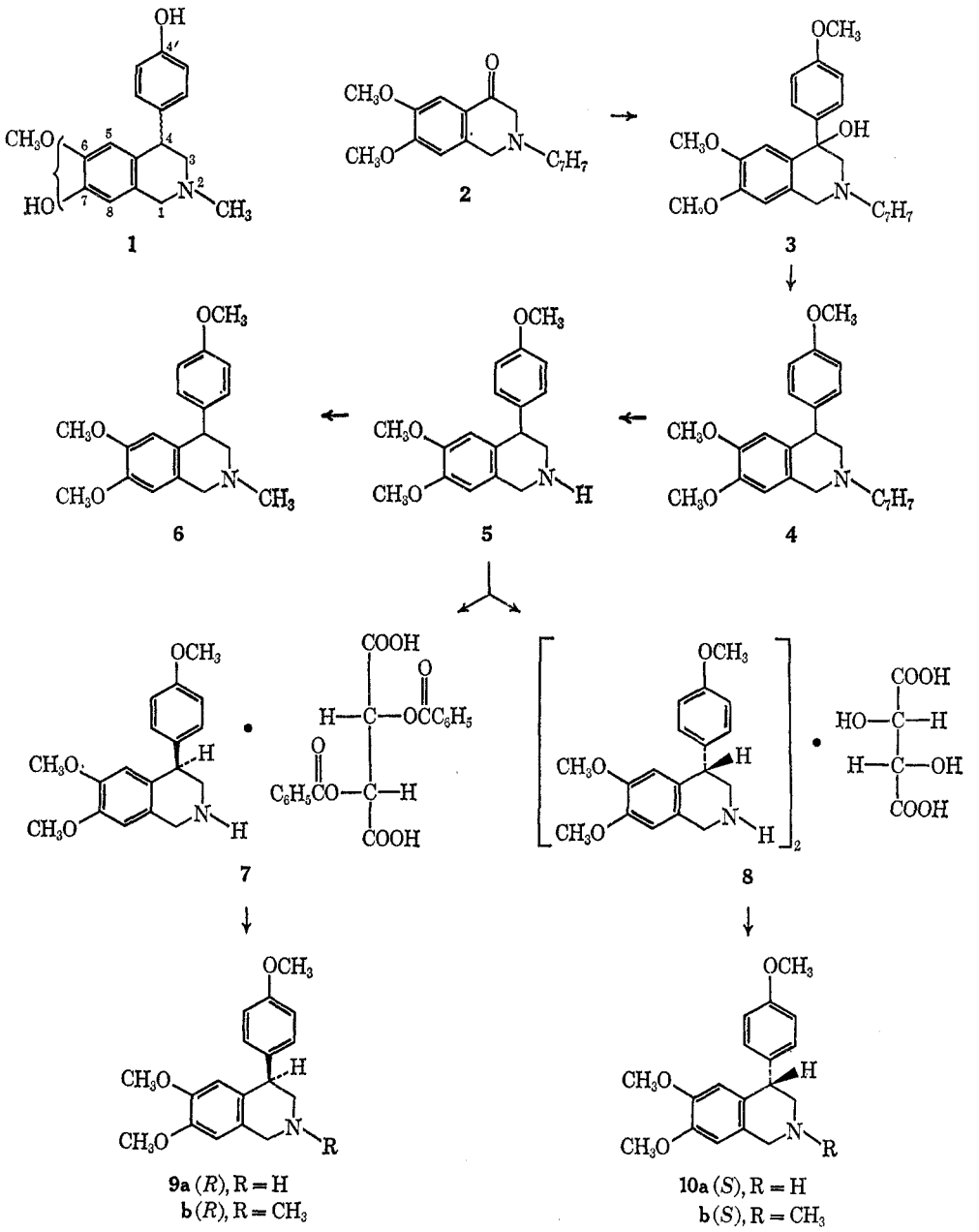
(1) We are grateful to the U. S. Public Health Service for partial support of this work (Grant He 7503).

(2) For a recent review, see W. C. Wildman in "The Alkaloids," Vol. XI, R. H. F. Manske, Ed., Academic Press Inc., New York, N. Y., 1968, Chapter 10.

(3) A comparison of cherylline and the phenolic alkaloid (crinin) isolated by H.-G. Boit, *Chem. Ber.*, **87**, 1704 (1954), has been performed by W. Döpke, Humboldt University, Berlin, who found the alkaloids to be identical. It is proposed that "crinin" should be referred to as cherylline to avoid confusion in the literature with crinine, a nonphenolic alkaloid.

(4) It was necessary to run the ir spectra in KBr pellets because of solubility problems. While the ir spectrum of an enantiomer frequently differs from that of the racemate when measured in the solid state, in this case the spectra are fortuitously superimposable and can be used as proof of chemical identity.

SCHEME I



The positions of the hydroxyl and methoxyl groups in ring A of cherylline were assigned by nmr spectroscopy. The spectrum in DMSO-d_6 shows two singlets at δ 6.23 and 6.49. Because of the shielding effect of the phenyl group at C-4, the signal at δ 6.23 is attributed to the proton at C-5 and the latter to the proton at C-8. On addition of a drop of NaOD in D_2O, both singlets are shifted upfield to δ 6.06, representing a shift of 10 and 26 Hz, respectively. Since on forming the phenolate the large upfield shift is observed for the proton at C-8, the hydroxyl group must be located at C-7.

The configuration of the alkaloid at the only asymmetric center (C-4) was determined by examination of the ORD and CD spectra of cherylline and of the two enantiomers of the O,O-dimethyl derivative, which were prepared in the following manner. Condensation of *p*-methoxyphenylmagnesium bromide with 2-benzyl-2,3-dihydro-6,7-dimethoxy-4(1H)-isoquinolone (**2**)[5] afforded the carbinol **3**, which was transformed by acid treatment and subsequent sodium borohydride reduction to the 4-phenyl-substituted tetrahydroisoquinoline **4**. Catalytic debenzylation of **4** gave the secondary amine **5**.[6] Reductive N-methylation of **5** provided (±)-O,O-dimethylcherylline hydrochloride (**6**·HCl), while resolution of **5** with dibenzoyl-*d*-tartaric acid and *l*-tartaric acid gave the diastereoisomers **7** and **8** which, on reductive N-methylation of the corresponding secondary amines **9a** and **10a**, were transformed to the respective enantiomers **9b** and **10b** (Scheme I).

The ORD curve of **9b** shows a positive Cotton effect at 294 mμ and the CD curve shows a maximum at 288 mμ. The ORD and CD spectra of **10b** are exact mirror

(5) G. Grethe, H. L. Lee, M. Uskoković, and A. Brossi, *J. Org. Chem.*, **33**, 491, 494 (1968).

(6) (a) This compound and the corresponding N-methyl derivative (**6**) were initially prepared by an alternate procedure by A. Rheiner, Jr., of F. Hoffmann-La Roche & Co., A. G., Basle, Switzerland; (b) A. Rheiner, Jr. *Helv. Chim. Acta*, in press.

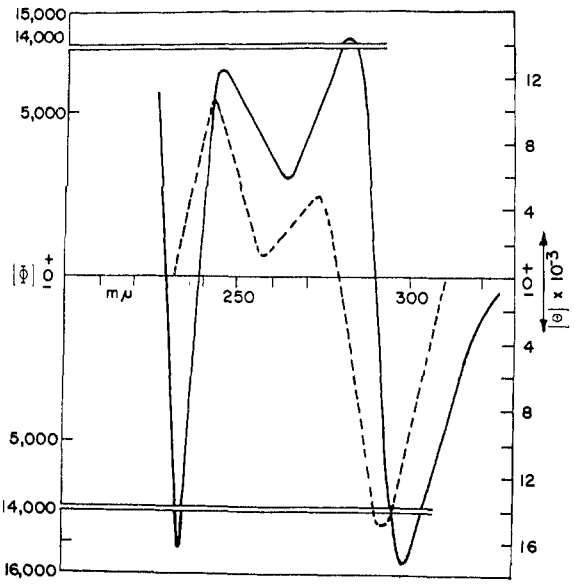
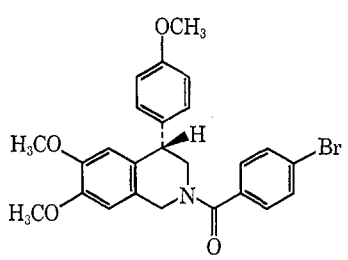
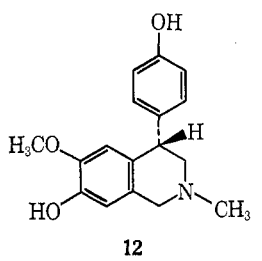


Figure 1.—ORD (—) and CD (---) curves of cherylline (**12**) (*c* 0.02, CH_3OH).

images of those of **9b**. By analogy to structural assignments of ORD spectra in the 4-aryltetralin (lignan) series,[7] the *R* configuration was assigned to **9a** and **9b** and the *S* configuration to the enantiomers **10a** and **10b**.[8] Comparison of the ORD and CD spectra of cherylline (Figure 1) with those of the synthetic compounds indicated that the alkaloid possesses the *S* configuration. The absolute configurations assigned above have been verified by an X-ray crystallographic study[8] of **11**. From this information cherylline can be assigned structure **12**.



11 (*S*)



12
cherylline

Experimental Section[9]

Isolation of Cherylline.—Ground, fresh bulbs of *Crinum powellii* var. *alba* (16.45 kg) were extracted several times with ethanol at 30°. The extract was filtered and evaporated under reduced pressure at 30° until turbidity appeared. The concentrate was diluted with water, acidified to pH 2 with tartaric acid, and extracted three times with benzene and three times with chloroform. Separate concentration of these extracts afforded 51.5 and 25.3 g of benzene- and chloroform-soluble materials, respectively. The aqueous solution was adjusted to pH 8 with ammonium hydroxide and extracted five times with chloroform. Evaporation of the chloroform extract under reduced pressure gave 33.2 g of alkaloidal material. Lycorine[2] (3.0 g, identified by melting point and ir spectra) precipitated during concentration of the chloroform. The aqueous raffinate was adjusted to pH 10 and extracted three times with chloroform. Concentration of the chloroform gave an additional 4.4 g of mainly alkaloidal material. One gram of the chloroform-soluble pH 8 extract was chromatographed by thick layer chromatography on 20 × 20 cm plates of silica gel PF (254 + 366) (0.5 mm). Development with chloroform–methanol–diethylamine (90:5:5) provided four bands, of which the second least mobile had major quantities of alkaloid.[10] This material was eluted from the silica gel with methanol and rechromatographed on the same support using ethyl acetate–methanol (70:30) as eluent. Nine distinct substances were observed. The two materials most mobile in the solvent system were in minor amounts; the last four (least mobile) components proved to be the expected major alkaloids, crinine and powelline. The intermediate fractions were crystallized initially from chloroform and then recrystallized from acetone to give 20 mg of cherylline: mp 217–218°; $[\alpha]^{26}D$ −69° (*c* 0.20, CH_3OH); uv max 225 mμ (ε 15,000) (sh), 280 (3960), 285 (4050), and 294 (2480)(sh). Basification of this ethanolic solution caused the maximum to shift to 299 mμ. Cherylline forms a hydrochloride, mp 238–239°, after recrystallization from acetone.

Treatment of cherylline in 95% ethanol with excess diazomethane at 0° for 1 week provided an O-methyl derivative which gave the same R_f values as **6** with three solvent systems, namely EtOAc–MeOH (70:30), EtOAc–MeOH (50:50), and $CHCl_3$–MeOH–$(C_2H_5)_2NH$ (92:3:5). Treatment of the O-methyl derivative with ethanolic HCl, concentration, and crystallization from acetone–methanol gave a hydrochloride, mp 229–230°, identical in chromatographic behavior and in ir (KBr) spectrum with synthetic **6**·HCl. A mixture of the two hydrochlorides showed no melting point depression.

Racemic 2-Benzyl-6,7-dimethoxy-4-(4-methoxyphenyl)-1,2,3,4-tetrahydro-4-isoquinolinol Hydrochloride (3·HCl).—To a stirred mixture of 2.4 g (0.1 mol) of dry magnesium turnings and a trace of iodine in 14 ml of dry tetrahydrofuran was added a solution of 21 g (0.112 mol) of *p*-bromoanisole in 14 ml of dry tetrahydrofuran over 10 min. The mixture was stirred and refluxed for 1 hr; then a solution of 25 g (0.084 mol) of 2-benzyl-2,3-dihydro-6,7-dimethoxy-4(1H)-isoquinolone (**2**), obtained by neutralization of the corresponding hydrochloride[5] in 200 ml of dry tetrahydrofuran was added over 10 min. The reaction mixture was stirred and refluxed for 4 hr, cooled, poured into 100 ml of an ice-cold, saturated solution of ammonium chloride, and extracted with three 100-ml portions of ether. The ether extracts were evaporated and the residue was dissolved in 200 ml of ethanol and rendered acidic with 6 *N* hydrochloric acid. The resulting white crystals were filtered, washed with ether, and dried to give 26 g (70%) of **3**·HCl, mp 178–181°. An analytical specimen was prepared from ethanol: mp 180–181°; uv max 225 mμ (ε 22,400) (sh), 275 (4720) (sh), 280 (4960), and 298 (3400) (sh); nmr δ 3.52 (s, 3, OCH_3-4′), 3.77 (s, 6, OCH_3-6, -7), 6.35 (s, 1, CH-5), 6.86 (s, 1, CH-8), 6.91 and 7.29 (AA′,BB′ pattern, 4, J = 10 Hz, CH-2′, CH-3′, CH-5′, CH-6′), and 11.35 (b, 1, $^+$NH).

Anal. Calcd for $C_{25}H_{27}NO_4$·HCl (mol wt, 441.96): C, 67.94; H, 6.39. Found: C, 67.99; H, 6.13.

Racemic 2-Benzyl-6,7-dimethoxy-4-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (4·HCl).—A solution of 20 g (0.045 mol) of **3** in 170 ml of 35% ethanolic hydrogen chloride was refluxed for 2 hr and evaporated under reduced pressure. The residue was dissolved in 300 ml of methanol, and 15 g (0.4

(7) P. Crabbé in "Advances in Stereochemistry," Vol. I, N. J. Allinger and E. L. Eliel, Ed., p 144, 1967, and references therein.

(8) V. Toome, J. F. Blount, G. Grethe, and M. Uskoković, Chemical Research Department, Hoffmann-La Roche Inc., Nutley, N. J. Details will be published elsewhere.

(9) Melting points of synthetic materials were taken in open capillary tubes with a Thomas–Hoover melting point apparatus; those of cherylline and derivatives were observed on a Kofler microscope hot stage. All melting points are corrected. Infrared spectra were determined either with a Beckman Infrared Model IR-9 or Model IR-12 spectrophotometer. The uv spectra were recorded on a Cary recording spectrophotometer, Model 14M, in ethanol unless noted to the contrary. 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 Model A-60 or HA-100 spectrophotometer using DMSO-d_6 as solvent unless otherwise indicated. Chemical shifts are reported in δ units using tetramethylsilane as internal reference. The following abbreviations are used in connection with the nmr data: s, singlet; cp, complex pattern; m, multiplet. The mass spectra were taken with a CEC 21-110 mass spectrometer at 70 eV using a direct insertion probe.

Extracts of products in organic solvents were washed with water and dried over anhydrous sodium sulfate.

(10) Meaningful R_f values could not be obtained because of variations in band width and migration.

mol) of sodium borohydride was added to the stirred solution over 30 min. The reaction mixture was stirred for 2 hr and evaporated. The residue was suspended in water and extracted with methylene chloride. The organic extract was evaporated and the residue was dissolved in ethanol and rendered acidic with ethanolic hydrogen chloride. Addition of ether afforded 13 g (68%) of **4**·HCl, mp 194–195°. An analytical sample was prepared from ethanol: mp 196–197°; uv max 225 mμ (ε 19,700) (sh), 278 (4620), 283 (4780), and 292 (3050) (sh); nmr δ 3.51 (s, 3, OCH_3-4′), 3.76 and 3.79 (s, 3 H each, OCH_3-6, -7), 6.23 (s, 1, CH-5), 6.83 (s, 1, CH-8), 6.96 and 7.17 (AA′BB′ pattern, 4, J = 9 Hz, CH-2′, CH-3′, CH-5′, CH-6′), and 12.1 (b, 1, $^+$NH).

Anal. Calcd for $C_{25}H_{27}NO_3$·HCl (mol wt, 425.96): C, 70.49; H, 6.63; N, 3.29. Found: C, 70.52; H, 6.80; N, 3.15.

Racemic 6,7-Dimethoxy-4-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (5) and Hydrochloride (5·HCl).—A mixture of 12.8 g (0.03 mol) of **4** and 3 g of 10% Pd–C in 20 ml of glacial acetic acid was hydrogenated at 50° under atmospheric pressure for 4 hr and cooled, and the catalyst was filtered. The filtrate was evaporated under reduced pressure and the residue was crystallized from methanol–ether to give 9 g (89%) of **5**, mp 230–231°. An analytical specimen was prepared from methanol–ether: mp 234–235°; uv max 227 mμ (ε 19,400), 278 (4660), 284 (4780), and 292 (3200)(sh); nmr δ 3.52 (s, 3, OCH_3-4′), 3.78 (s, 6, OCH_3-6, -7), 6.27 (s, 1, CH-5), 6.90 (s, 1, CH-8), 6.94 and 7.17 (AA′BB′ pattern, 4, J = 9 Hz, CH-2′, CH-3′, CH-5′, CH-6′), and 10.0 (b, 2, $^+NH_2$).

Anal. Calcd for $C_{18}H_{21}NO_3$·HCl (mol wt, 335.84): Cl, 10.56. Found: Cl, 10.60.

An aliquot of **5**·HCl was dissolved in water, rendered alkaline with ammonium hydroxide, and extracted with methylene chloride. The organic extract was evaporated and the residue was recrystallized twice from ether to afford **5**, mp 91–92°.

Anal. Calcd for $C_{18}H_{21}NO_3$ (mol wt, 299.37): C, 72.22; H, 7.07; N, 4.68. Found: C, 72.01; H, 6.80; N, 4.30.

Racemic 6,7-Dimethoxy-4-(4-methoxyphenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (6·HCl).—A mixture of 9.85 g (0.033 mol) of **5** in 20 ml (0.52 mol) of 98–100% formic acid and 10 ml (0.13 mol) of 37% formaldehyde was heated at 100° for 3 hr and refluxed for 8 hr, and the volatiles were evaporated under reduced pressure. The residue was dissolved in water, rendered alkaline with 5% sodium hydroxide, and extracted with methylene chloride. The organic extract was evaporated, and the residue was dissolved in ethanol, acidified with ethanolic hydrogen chloride, and evaporated. The resulting solid was recrystallized twice from methanol–ether to give 6.3 g (55%) of **6**·HCl: mp 228–229°; uv max 226 mμ (ε 19,000), 276 (4460), 282 (4600), and 290 (2950)(sh); nmr δ 2.89 (s, 3, NCH_3), 3.53 (s, 3, OCH_3-4′), 3.80 (s, 6, OCH_3-6, -7), 6.27 (s, 1, CH-5), 6.85 (s, 1, CH-8), and 6.95 and 7.17 (AA′BB′ pattern, 4, J = 9 Hz, CH-2′, CH-3′, CH-5′, CH-6′).

Anal. Calcd for $C_{19}H_{23}NO_3$·HCl (mol wt, 349.87): C, 65.23; H, 6.92; Cl, 10.13. Found: C, 65.57; H, 7.12; Cl, 10.22.

(+)-6,7-Dimethoxy-4(*R*)-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (9a).—To a solution of 5.245 g (15.6 mmol) of **5**·HCl in methanol was added 845 mg (15.6 mmol) of sodium methoxide. The solvent was removed under reduced pressure and the residue was extracted three times with dichloromethane. The combined extracts were filtered and evaporated to dryness under reduced pressure. The resulting free base was dissolved in 15 ml of ethanol and combined with a solution of 5.6 g (15.6 mmol) of dibenzoyl-*d*-tartaric acid in 15 ml of ethanol. The crystalline material (6.2 g) which precipitated from this solution on standing at room temperature was recrystallized twice from methanol to give 3.4 g (66%) of the dibenzoyl-*d*-tartrate (**7**): mp 186–188°; $[\alpha]^{25}D$ −45.8° (*c* 1.03, MeOH). An analytical sample, after recrystallization from methanol and drying at 75° for 24 hr, showed the following physical properties: mp 191–193°; $[\alpha]^{25}D$ −45.8° (*c* 1.0, MeOH); ORD (*c* 0.164, MeOH) $[\alpha]_{317}$ −360° (tr), $[\alpha]_{304}$ 0°, $[\alpha]_{293}$ +1090° (pk), $[\alpha]_{288}$ 0°, $[\alpha]_{276}$ −6200° (tr), $[\alpha]_{265}$ −4560° (pk), $[\alpha]_{243}$ −20,000° (tr), $[\alpha]_{236}$ 0°, $[\alpha]_{227}$ +28,600° (pk), and $[\alpha]_{210}$ +6700°; CD $[\Theta]_{300}$ 0, $[\Theta]_{287}$ +36,960, $[\Theta]_{278}$ 0, $[\Theta]_{271}$ −17,160, $[\Theta]_{262}$ −18,480, $[\Theta]_{238}$ −27,060, $[\Theta]_{228}$ 0, $[\Theta]_{223}$ +95,040.

Anal. Calcd for $C_{18}H_{21}NO_3 \cdot C_{18}H_{14}O_8$ (mol wt, 657.65): C, 65.75; H, 5.36; N, 2.13. Found: C, 65.51; H, 5.44; N, 2.14.

To an aqueous solution of 3.2 g of **7** was added excess 6 *N* sodium hydroxide and the free base was extracted with chloroform. The combined extracts were washed with water, dried (Na_2SO_4), and evaporated to dryness. The crystalline residue, after recrystallization from ether, afforded in several crops a total of 1.074 g (41%) of the free base (**9a**): mp 110–112°; $[\alpha]^{25}D$ +36° (*c* 1.05, MeOH). An analytical sample from a previous experiment, after recrystallization from ether and drying at 55° for 70 hr under reduced pressure, showed the following physical properties: mp 108–110°; $[\alpha]^{25}D$ +38.4° (*c* 1.22, MeOH); ORD (*c* 0.292, MeOH) $[\alpha]_{293}$ +3420° (pk), $[\alpha]_{287}$ 0°, $[\alpha]_{277}$ −6150° (tr), $[\alpha]_{261}$ −1760° (pk), $[\alpha]_{243}$ −5820° (tr), $[\alpha]_{236}$ 0°, $[\alpha]_{227}$ +13,000° (pk), $[\alpha]_{218}$ 0°, $[\alpha]_{214}$ −1470° (tr), $[\alpha]_{211}$ 0°, and $[\alpha]_{210}$ +2060°; CD $[\Theta]_{310}$ 0, $[\Theta]_{288}$ +21,683, $[\Theta]_{278}$ 0, $[\Theta]_{272}$ −6776, $[\Theta]_{267}$ −2032, $[\Theta]_{239}$ −38,532, $[\Theta]_{232}$ 0, $[\Theta]_{224}$ +29,744, and $[\Theta]_{212}$ +12,168; ir ($CHCl_3$) *ca.* 3300 (broad, NH), 1615, 1585, 1515 and 1468 (phenyl), and 1255 cm^{-1} (OCH_3); uv max (MeOH) 236–237 mμ (ε 20,600), 279–280 (5070), and 284–285 (5060); nmr ($CDCl_3$) δ 2.70 (broad, s, 1, -NH), 2.9–3.5 (cp, 2, CH_2-3), 3.68, 3.78, 3.86 (s, 3 each, OCH_3), 4.04 (s, 2, CH_2-1), *ca.* 3.9 partially hidden underneath other signals (m, 1, CH-4), 6.38 (s, 1, CH-5), 6.56 (s, 1, CH-8), and 6.83 and 7.02 (AA′BB′ pattern, 4, J = 9 Hz, CH-2′, CH-3′, CH-5′, CH-6′); mass spectrum (70 eV) *m/e* (rel intensity) 299 (30), 270 (35), 239 (100), 209 (25), 195 (25), 183 (45), 165 (45), 152 (45), 141 (35), 121 (30), 115 (45), 91 (30), and 77 (45).

Anal. Calcd for $C_{18}H_{21}NO_3$ (mol wt, 299.36): C, 72.21; H, 7.07; N, 4.68. Found: C, 72.09; H, 7.05; N, 4.45.

(−)-6,7-Dimethoxy-4(*S*)-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (10a).—The mother liquors from the crystallization of **7** were combined and evaporated to dryness. The residue was taken up in water, excess sodium hydroxide was added to the aqueous solution, and the free base was extracted with chloroform. The combined organic layer was washed with water, dried, and evaporated to dryness. The residue (2.375 g) was dissolved in 15 ml of ethanol. Addition of 1.15 g of *l*-tartaric acid in 15 ml of ethanol afforded a crystalline salt. After two recrystallizations from methanol the tartrate (**8**) weighed 2.1 g, $[\alpha]^{25.4}D$ −59° (*c* 1.27, H_2O), mp 183–184° dec. To an aqueous solution of **8** was added excess 6 *N* sodium hydroxide, and the liberated free base was extracted with three portions of chloroform. The combined organic layer was washed with water, dried, and evaporated to dryness to give, after recrystallization from ether, 0.9 g (34%) of **10a**, mp 110–112°. An analytical sample, after recrystallization from ether, showed the following physical properties: mp 111–113°; $[\alpha]^{25}D$ −38.2° (*c* 1.12, MeOH); ORD (*c* 0.292, MeOH) $[\alpha]_{293}$ −3700° (tr), $[\alpha]_{287}$ 0°, $[\alpha]_{277}$ +6040° (pk), $[\alpha]_{261}$ +1540° (tr), $[\alpha]_{242}$ +5620° (pk), $[\alpha]_{238}$ 0°, $[\alpha]_{228}$ −17,000° (tr), and $[\alpha]_{217}$ −3020° (pk); CD $[\Theta]_{310}$ 0, $[\Theta]_{289}$ −22,022, $[\Theta]_{278}$ 0, $[\Theta]_{272}$ +6098, $[\Theta]_{257}$ +1694, $[\Theta]_{238}$ +45,292, $[\Theta]_{232}$ 0, $[\Theta]_{224}$ −34,476, and $[\Theta]_{214}$ −6760.

Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.20; H, 7.20; N, 4.70.

(+)-6,7-Dimethoxy-2-methyl-4(*R*)-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (9b).—A solution of 950 mg of **9a** and 2.82 ml of 37% formaldehyde in 30 ml of methanol was allowed to stand at room temperature for 4 hr. The mixture was then hydrogenated at 1 atm over Raney nickel at room temperature overnight. The catalyst was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in ether, insoluble material was removed by filtration, and petroleum ether (bp 30–60°) was added to the filtrate to afford 651 mg (65%) of crystalline N-methylated product (**9b**), mp 83–85°. Recrystallization from ether–petroleum ether gave 527 mg of analytically pure **9b**: mp 87–89° (after drying under reduced pressure for 4 days at 40°); $[\alpha]^{24.9}D$ +21.58° (*c* 1.01, MeOH); ORD (*c* 0.313, MeOH) $[\alpha]_{294}$ +3960° (pk), $[\alpha]_{287}$ 0°, $[\alpha]_{278}$ −6250° (tr), $[\alpha]_{263}$ −2040° (pk), $[\alpha]_{243}$ −6060° (tr), $[\alpha]_{237}$ 0°, $[\alpha]_{229}$ +13,550° (pk), $[\alpha]_{221}$ 0°, $[\alpha]_{214}$ −4150° (tr), and $[\alpha]_{211}$ −3090°; CD $[\Theta]_{304}$ 0, $[\Theta]_{288}$ +23,670, $[\Theta]_{278}$ 0, $[\Theta]_{272}$ −5940, $[\Theta]_{257}$ −1980, $[\Theta]_{244}$ −15,180, $[\Theta]_{235}$ 0, $[\Theta]_{227}$ +71,280, $[\Theta]_{214}$ +7920, $[\Theta]_{205}$ +95,040, $[\Theta]_{200}$ 0, and $[\Theta]_{196}$ −60,720; ir ($CHCl_3$) 2790, 2770 (Bohlmann bands), 1610, 1585, 1515 and 1465 (phenyl), and 1265 and 1255 cm^{-1} (OCH_3); uv max (MeOH) 225 mμ (ε 20,600), 277 (5000), 283 (5020), and 290 (3400)(sh); nmr ($CDCl_3$) δ 2.42 (s, 3, NCH_3), 2.4–3.2 (cp, 2, CH_2-1), 3.66, 3.80, 3.88 (s, 3 H each, OCH_3), 3.5–4.4, partially hidden beneath OCH_3 signals (cp, 3, CH_2-3 and CH-4), 6.38 (s, 1, CH-5), 6.59 (s, 1, CH-8), and 6.85 and 7.12 (AA′BB′ pattern, 4, J = 9 Hz, CH-2′, CH-3′, CH-5′, CH-6′); mass spectrum (70 eV) *m/e* (rel intensity) 313 (25), 270 (47), 239 (100), 224 (7), 208 (8), 195 (7), 181 (6), 165 (10), 151 (8), and 135 (17).

Anal. Calcd for $C_{19}H_{23}NO_3$ (313.38): C, 72.82; H, 7.40; N, 4.47. Found: C, 73.04; H, 7.60; N, 4.44.

(−)-6,7-Dimethoxy-2-methyl-4(*S*)-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (10b).—Reductive N-methylation of 850 mg of **10a** as described in the previous experiment afforded 636 mg (71%) of **10b**, mp 83–85°, after crystallization from ether–petroleum ether. Recrystallization from the same solvent mixture gave 400 mg of analytically pure **10b**, mp 87–88°, after drying under reduced pressure at 40° for 4 days: $[\alpha]^{24.9}D$ −21.65° (*c* 0.965, MeOH); ORD (*c* 0.3134, MeOH), $[\alpha]_{294}$ −3960° (tr), $[\alpha]_{288}$ 0°, $[\alpha]_{279}$ +6760° (pk), $[\alpha]_{264}$ +2170° (tr), $[\alpha]_{244}$ +5750° (pk), $[\alpha]_{239}$ 0°, $[\alpha]_{232}$ −15,900° (tr), $[\alpha]_{222}$ 0°, $[\alpha]_{217}$ +4470° (pk), and $[\alpha]_{215}$ +2870°; CD $[\Theta]_{304}$ 0, $[\Theta]_{288}$ −24,090, $[\Theta]_{278}$ 0, $[\Theta]_{272}$ +5610, $[\Theta]_{267}$ +1980, $[\Theta]_{248}$ +14,850, $[\Theta]_{234}$ 0, $[\Theta]_{226}$ −68,640, $[\Theta]_{214}$ −5280, $[\Theta]_{205}$ −102,960, $[\Theta]_{200}$ 0, and $[\Theta]_{197}$ +58,080.

Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.77; H, 7.51; N, 4.49.

(+)-2-(4-Bromobenzoyl)-6,7-dimethoxy-4(*S*)-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (11).—To a stirred solution of 299 mg (1 mmol) of **10a** in 20 ml of benzene was added a solution of 300 mg (2.2 mmol) of potassium carbonate in 5 ml of water followed by the portionwise addition of 500 mg (2.3 mmol) of 4-bromobenzoyl chloride. After the addition was complete, stirring was continued for 2 hr. The benzene layer was separated and washed successively with 6 *N* sodium hydroxide, three portions of 2 *N* hydrochloric acid, and water. After drying (Na_2SO_4) and evaporation, the crystalline residue was washed with ether to give 323 mg (67%) of **11**, mp 158–160°. A sample was recrystallized from ether to afford analytically pure **11** as long needles: mp 159–161°; $[\alpha]^{24}D$ +120.3° (*c* 1.28, $CHCl_3$); ir ($CHCl_3$) 1630 (amide C=O), 1615 (sh), 1590, 1510, and 1460 (phenyl), and 1260 cm^{-1} (OCH_3); uv max (CH_3OH) 226 mμ (ε 35,500), 278 (6270), 283–284 (6060), and 291–292 (3800)(sh); nmr ($CDCl_3$) δ 3.72, 3.82, and 3.90 (s, 3 H each, OCH_3) 4.67 and 5.10 (cp, 2 H each, CH_2NCH_2), and 6.3–7.2 (cp, 10, aromatic H); ORD (*c* 0.482, methanol) $[\alpha]_{301}$ +1310° (pk), $[\alpha]_{291}$ +1240° (tr), $[\alpha]_{274}$ +26,000° (pk), $[\alpha]_{243}$ 0°, $[\alpha]_{225}$ −21,300° (tr), $[\alpha]_{218}$ −13,000° (sh), and $[\alpha]_{203}$ 0°; CD $[\Theta]_{300}$ 0, $[\Theta]_{288}$ −13,200, $[\Theta]_{271}$ 0, $[\Theta]_{238}$ +125,400, $[\Theta]_{228}$ 0, $[\Theta]_{208}$ −75,900, and $[\Theta]_{200}$ 0; mass spectrum (70 eV) *m/e* (rel intensity) 483 (30), 481 (30), 403 (5), 373 (5), 282 (20), 270 (45), 239 (100), 183 (30), and 121 (30).

Anal. Calcd for $C_{25}H_{24}BrNO_4$ (mol wt, 482.40): C, 62.25; H, 502; N, 2.90. Found: C, 62.25; H, 4.75; N, 3.20.

Registry No.—**3**·HCl, 23349-28-2; **4**·HCl, 23349-29-3; **5**, 23349-30-6; **5**·HCl, 23349-31-7; **6**·HCl, 23349-32-8; **7**, 23330-74-7; **9a**, 23330-75-8; **9b**, 23330-76-9; **10a**, 23330-77-0; **10b**, 23367-60-4; **11**, 23330-78-1; **12**, 23367-61-5; **12**·HCl, 23330-44-1.

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Constituents of *Eurycoma longifolia* Jack

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Investigation of the constituents of *Eurycoma longifolia* Jack, obtained from several regions of Viet Nam, has resulted in the isolation of two steroids, namely β-sitosterol and campesterol, 2,6-dimethoxybenzoquinone, and a bitter principle called eurycomalactone (**1a**). Eurycomalactone is closely related to the other bitter principles previously encountered in the family *Simaroubaceae*. Eurycomalactone is the first compound of this series with a keto group at C-6 and a γ-lactone group between positions 14 and 7. The configuration is discussed. Dihydroeurycomalactone (**2a**) is also isolated from the bark of *Eurycoma longifolia* originated from Dinh-Quan.

Numerous plants of the *Simaroubaceae* are known in herbal medicine for their therapeutic activities, and several of them have been shown to be effective antiamebic agents.[2] Various studies on the bitter principles occurring in several genera of the family *Simaroubaceae* have shown that they belong to a group of structurally related compounds with close chemical and botanical relationships to each other.[3]

This work describes the investigation of the chemical constituents of *Eurycoma longifolia* Jack, a bush which is common in Viet Nam, especially around Bien-Hoa, Trang-Bom, and Dinh-Quan. Its local name is "cây bá binh" (tree which cures hundred of diseases), and its bark is used in the Vietnamese pharmacopaeia.

Chromatography of the bark afforded, besides β-sitosterol and campesterol, characterized as their acetates (see Experimental Section), eurycomalactone (**1a**) and 2,6-dimethoxybenzoquinone, which is a common chemical constituent of the Simaroubaceae family.[4]

Eurycomalactone (**1a**)[5] was also isolated from extracts of the leaves of *Eurycoma longifolia* (albeit in a much lower yield, *ca.* 10%) and analyzed for $C_{19}H_{24}O_6$. This was confirmed by its mass spectrum. Its infrared (ir) spectrum showed bands for hydroxyls, a saturated and an α,β-unsaturated ketone, and a γ-lactone grouping. The ultraviolet (uv) spectrum confirms the presence of a conjugated keto chromophore, which seemed to be homoconjugated with a saturated carbonyl. The nuclear magnetic resonance (nmr) spectrum showed resonances for four methyl groups, one secondary methyl, one vinylic methyl, and two tertiary methyls (see Experimental Section). A signal integrating for one vinylic proton appeared at 6.1 ppm, and a resonance for one proton situated on a carbon-bearing oxygen atom is observed at 4.8 ppm. Finally, eurycomalactone (**1a**) gives a mono- and a bis-2,4-dinitro-

(1) Taken in part from the D.Sc. Thesis of N.-N.-S. For a preliminary communication, see Le-Van-Thoi, Nguyen-Ngoc-Suong, and P. Crabbé, *Chem. Commun.*, 821 (1969).

(2) T. A. Geissman, *Ann. Rev. Pharmacol.*, **4**, 305 (1964).

(3) For a review of the literature on simaroubaceous plants, see J. Polonsky, *Planta Med. Suppl.*, 107 (1966).

(4) See, among others, (a) J. Polonsky and E. Lederer, *Bull. Soc. Chim Fr.*, 1157 (1959); (b) W. Karrer, *Helv. Chim. Acta*, **13**, 1424 (1930); (c) D. J. Cosgrove, D. G. H. Daniels, E. N. Greer, J. B. Hutchinson, T. Moran, and J. K. Whitehead, *Nature*, **169**, 966 (1952); (d) D. J. Cosgrove, D. G. Daniels, K. J. Whitehead, and J. D. S. Goulden, *J. Chem. Soc.*, 4821 (1952).

(5) Preliminary communications on the isolation of this substance have already appeared: (a) Le-Van-Thoi and Nguyen-Ngoc-Suong, *Ann. Fac. Sci. Saigon*, 89 (1962); (b) Le-Van-Thoi and Nguyen-Ngoc-Suong, International Symposium on the Chemistry of Natural Products, Kyoto, April 1964, Abstracts of Papers, p 51.