1 and 2 solidified (0.3 g) and were recrystallized from acetone–benzene–petroleum ether to give a new sesquiterpene lactone which had mp 203–206°, infrared bands ($CHCl_3$) at 3700 and 3500 (broad, OH), 1770 (γ-lactone), 1725 (broad, double-intensity), shoulders at 1660 and 1650 cm^{-1} (double bands); intense end absorption at 205–210 mμ. Fractions 3 and 4 yielded additional small quantities of this substance.

Anal. Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 62.88; H, 7.32.

Fraction 6 on solution in acetone and addition of petroleum ether yielded 0.1 g of crystalline material which after recrystallization from acetone–ether–petroleum ether melted at 255–256° and was identified as spathulin.

Extraction of *Gaillardia parryi* Greene.—Dried, above-ground material (3 lb), collected in July 1962, by Dr. W. P. Stoutamire (WPS No. 3991) along Utah State Road 64 between St. George, Utah, and Wolf Hole, Ariz., a few miles south of the Arizona line was extracted with chloroform and worked up as usual. The residual crude gum (25 g) was dissolved in benzene–chloroform (1:3) and chromatographed over 350 g of alumina (Alcoa F-20, washed with ethyl acetate and dried at 140° for 1 hr), using six 200-ml fractions of benzene–chloroform (8.3 g of gum), seven 200-ml fractions of chloroform (2.9 g of solid which was homogeneous by thin layer chromatography), and chloroform–methanol (9:1, 1.1 g of solid identical with the previous material). Recrystallization of the solid fractions from acetone–isopropyl ether furnished 3.1 g of flexuosin A, mp 225°, identical with authentic material by R_f, mixture melting point, and infrared spectrum. Repeated rechromatography of the first eluate gave largely gummy material and in the more polar fractions additional small amounts of flexuosin A.

Registry No.—**1a**, 7706-45-8; **1b**, 7699-92-5; **2a**, 7699-93-6; **2b**, 7699-94-7; **3a**, 7699-95-8; **4a**, 7699-96-9; **5**, 7699-97-0; **6**, 7699-98-1; flexuosin A, 1381-28-8; **9**, 10035-79-7.

Acknowledgment.—We are grateful to Dr. W. P. Stoutamire, Dr. S. C. Harvey, and the late Dr. H. F. L. Rock for plant material and valuable correspondence, and the Florida State University for a grant-in-aid to help defray the cost of collections.

A Total Synthesis of Optically Active Lupinine without Benefit of Resolution

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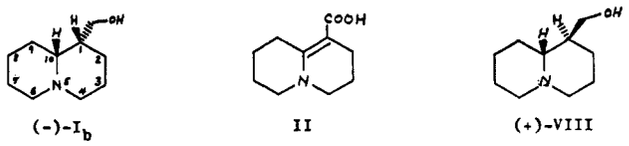
Synthesis of the optically active natural product lupinine has been achieved directly, without a separate resolution step. Sodium borohydride reductions of (−)- and (+)-1-menthoxycarbonyl-1(10)-dehydroquinolizidines gave (−)- and (+)-1-menthoxycarbonylquinolizidines, respectively, as the predominant isomers. Subsequent treatment with lithium aluminum hydride yielded (+)- and (−)-lupinines, respectively, in near 10% optical yields. Deuterium-labeling experiments showed C-10 in the unsaturated esters to be the site of hydride delivery. The observed asymmetric selection and the configurational relationships involved are accounted for with topological transition state models.

The absolute configuration of (−)-lupinine was established as (1*R*,10*R*)-1-hydroxymethylquinolizidine (Ib),[1] and, while racemic lupinine has been synthesized in a number of laboratories,[2] we have chosen this system, with its two asymmetric carbons, as the goal of a total synthesis which would include, in the chemical reactions used to attain the desired bonding sequence, features to impart asymmetric selection, so that the synthetic material might be produced in a predominant enantiomeric form without a separate resolution step. The concept required development of a synthesis scheme which would include an intermediate containing an atom, not to become part of the lupinine bonding sequence, but with a fixed configurational arrangement which could be used to influence the configuration of one of the asymmetric centers (C-1 or C-10) in lupinine as the latter was formed. The new asymmetric atom, thus formed in a predominant configuration, would then in turn influence formation of the second asymmetric atom in lupinine. Finally, the originally present atom of fixed configuration would subsequently be removed en route to lupinine. We concluded that an optically active ester of 1-carboxy-1(10)-dehydroquinolizidine (II) would fulfill these requirements, and we were able to obtain optically active synthetic lupinine in this manner.



(-)-I_b II (+)-VIII

The enantiomeric 1-menthoxycarbonyl-1(10)-dehydroquinolizidines (IIIa and IIIb) were individually prepared (Scheme I) by allowing 1(10)-dehydroquinolizidine (IV) to react with each of the enantiomeric menthyl chloroformates (Va and Vb). The details of the preparation of quinolizidine (VI), from which IV was prepared by mercuric acetate dehydrogenation[3] of the former, are given in the Experimental Section. Also given are the details of the preparations of each enantiomeric menthyl chloroformate (Va and Vb) which were obtained *via* reaction of enantiomeric menthol with phosgene in the presence of quinoline.

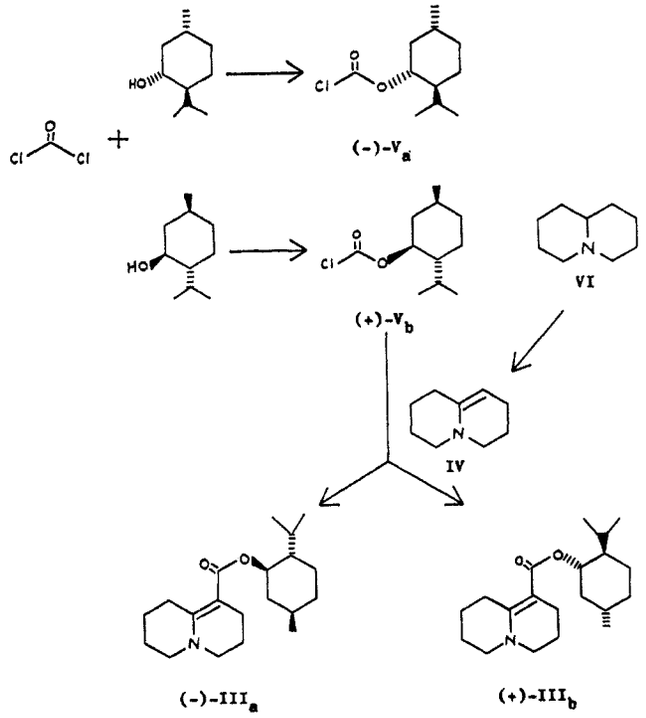
Treatment of each of enantiomeric unsaturated esters (−)-IIIa and (+)-IIIb with sodium borohydride in methanol (Scheme II) produced the saturated esters, (−)-VIIa and (+)-VIIb, respectively. The predominant isomer obtained from reduction of (−)-IIIa was (−)-VIIa, while (+)-VIIb was the predominant product obtained from (+)-IIIb. These assignments were clearly established by means of conversion of

(1) For an account of the experimental work upon which this was based, see N. J. Leonard in "The Alkaloids," R. H. F. Manske, Ed., Academic Press Inc., New York, N. Y., 1960, pp 264, 265.

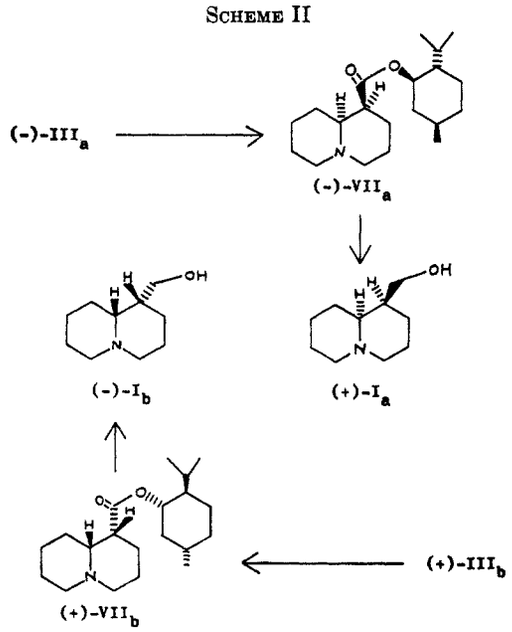
(2) G. R. Clemo, W. McG. Morgan, and R. Raper, *J. Chem. Soc.*, 965 (1937); K. Winterfeld and H. von Cosel, *Arch. Pharm.*, **278**, 70 (1940); V. Boekelheide and J. P. Lodge, Jr., *J. Am. Chem. Soc.*, **73**, 3681 (1951); V. Boekelheide, W. J. Linn, P. O'Grady, and M. Lamborg, *ibid.*, **75**, 3243 (1953); J. Ratusky and F. Sorm, *Chem. Listy*, **47**, 1491 (1953); *Collection Czech. Chem. Commun.*, **19**, 340 (1954); H. R. Lewis and C. W. Shoppee, *J. Chem. Soc.*, 313 (1956).

(3) N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. Gash, *J. Am. Chem. Soc.*, **77**, 439 (1955).

SCHEME I



SCHEME II

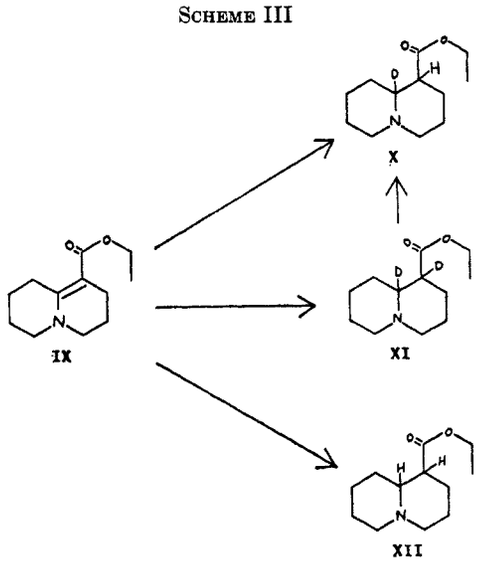


each series to lupinine. Thus, the levorotatory product [predominantly (−)-VIIa] obtained from (−)-IIIa gave, upon reduction by lithium aluminum hydride, dextrorotatory lupinine, (+)-Ia. On the basis of specific rotation values—$[\alpha]_D$ −20.9° (ethanol) for natural lupinine,[4] and $[\alpha]_D$ +2.10° (ethanol) for the reduction product of (−)-VIIa—an optical yield near 10% was indicated. The dextrorotatory unsaturated ester [(+)-IIIb] also gave rise to optically active lupinine [(−)-Ib] in near 10% optical yield—$[\alpha]_D$ −2.02° (ethanol).

In both cases, as well as in the other reductions of this study, the product was carefully examined (see the Experimental Section) for the presence of epilupinine (VIII). The complete absence of epilupinine in these reduction products[5] must be taken to mean that the menthoxycarbonyl group influences the configuration of the first-to-be-formed asymmetric atom only to the extent of about 10%, but that the stereospecificity for the formation of the second asymmetric atom is complete (100%).

The site (C-1 or C-10) of hydride delivery in the sodium borohydride reduction of the unsaturated ester under neutral conditions was determined to be C-10 (Scheme III). 1-Carbethoxy-1(10)-dehydroquinolizidine (IX) was treated with sodium borodeuteride in methanol-*d*, followed by hydrolysis with water. Deuterium was shown to be at C-10 in the product, ethyl lupininate (X), in two ways. First, the deuterium in X (ν_{CD} 2150 and 2000 cm^{-1}) was not removed after the ester was stirred during 24 hr in ethanolic sodium ethoxide. In addition, ethyl lupininate-1,10-d_2 (XI), prepared from IX by reduction with sodium borodeuteride in methanol-*d* and hydrolysis with deuterium oxide, gave ethyl lupininate-10-*d* by treatment of the former with ethanol and sodium ethoxide. The infrared CD absorption pattern of this authentic C-10 deuterio ester was identical with that of the initially obtained deuterio ester (both different from that of XI and XII).

SCHEME III



A transition state, topological explanation of the asymmetric selection observed in the present syntheses of the optically active lupinines, may be obtained by formulation of the lowest energy (conformation) pathway for delivery of hydride to C-10 in enantiomeric unsaturated esters (−)-IIIa and (+)-IIIb. Based on the reasonable assumption that the most serious nonbonded interactions of the groups attached to the carbinol carbon in the menthoxy portion are with the carbonyl oxygen, then the most favorable conformer is the one in which the smallest group, hydrogen, eclipses the carbonyl oxygen. That conformation is illustrated (XIII) in Scheme IV with (−)-1-menthoxycarbonyl-1(10)-dehydroquinolizidine. The isopropyl group extends out over the carbon–carbon double bond, making approach for the reagent more favorable from the

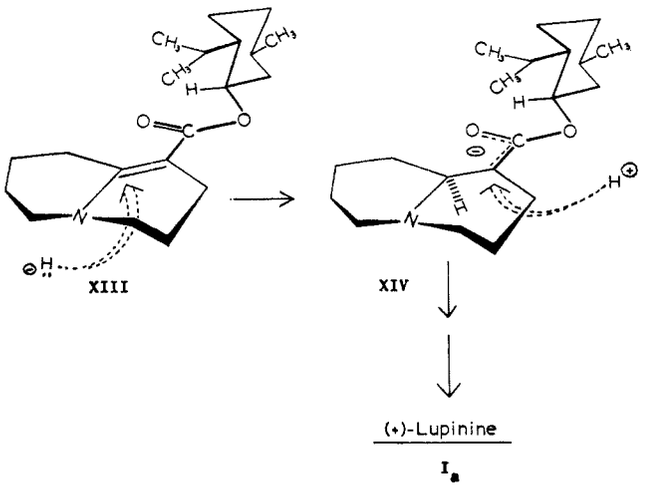
(4) N. K. Leonard in "The Alkaloids," Vol. III, R. H. F. Manske and H. L. Holmes, Ed., Academic Press Inc., New York, N. Y., 1953, Chapter 19.

(5) The same stereospecificity was observed by Bohlmann and Schmidt[6] when they reduced 1-carbethoxy-1(10)-dehydroquinolizidine (IX) and obtained only racemic lupinine.

(6) F. Bohlmann and O. Schmidt, *Chem. Ber.*, **97**, 1354 (1964).

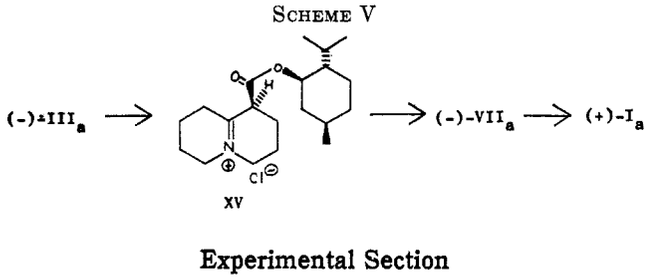
underside of the molecule as pictured. After hydride is delivered to C-10, the resulting enolate anion (XIV) is protonated at C-1. Formation of the second asymmetric carbon (C-1) is, however, completely stereospecific (proton attached *cis* to hydrogen at C-10). The predominant isomeric saturated ester, (−)-VIIa, would then have the configuration shown, and this is consistent with the fact that (+)-lupinine (Ia) is obtained upon lithium aluminum hydride reduction of the former.

SCHEME IV



In another series of experiments unsaturated ester (−)-IIIa was converted to its hydrochloride salt before reduction with sodium borohydride. Since the enamine must undergo protonation at C-1 in conversion to the eninium chloride (XV), it was expected that the menthoxy group would influence the steric course of the protonation at C-1 in a similar way that it influences hydride bonding to C-10. This was indeed the case since reduction of the resulting saturated ester also gave (+)-lupinine (Ia) as the predominate enantiomer. The optical yield in this reduction, however, was found to be 6.8%, lower than those observed in the neutral reductions. The difference in optical yields may be taken as a direct reflection of the fact that in the neutral reduction a rather bulky species (BH_4^-) initially attacks, while in salt formation it is a proton which initially adds to the molecule (Scheme V).

SCHEME V



Experimental Section

General—Temperatures are uncorrected. Combustion analyses were by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Infrared spectra were determined with a Perkin-Elmer Model 337 grating spectrometer. Nuclear magnetic resonance spectra were recorded at 60 Mc on a Varian A-60 spectrometer near room temperature, using chloroform-*d* solvent containing 4% (v/v) tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported under the δ convention in parts per million (ppm) relative to TMS (0 ppm). Polarimeter measurements were carried out with an O. C. Rudolph and Sons, Inc. (Caldwell, N. J.) instrument, Model 80, sodium light source.

Quinolizidine (VI).—The procedure of Boekelheide and Rothchild[7] was followed in that 1,1-dicarbethoxy-3-(2-pyridyl)-propane was prepared[7] and treated with hydrogen (250 atm) over copper chromite catalyst at 260°. This procedure, even after several attempts, however, was found to be unsatisfactory. Careful fractional distillation of the basic material obtained from the hydrogenation gave a major fraction [bp 79–83° (18–20 mm)] and a minor fraction [bp 100° (1.5 mm)]. The minor fraction was identified as 4-quinolizidone by comparison of the infrared spectrum determined from it with that of authentic 4-quinolizidone (see below). The major fraction did not appear to be quinolizidine because it gave a picrate salt which did not melt (mp 163–166°) as reported[7] (mp 198–199°) for quinolizidine picrate. Chromatographic examination[8] of the major fraction revealed the presence of two components in 3:2 ratio which, under the best conditions of temperature and helium flow rate, were 12 min apart. A sample of each component was collected and examined spectroscopically. The greater component was identified as quinolizidine, while the lesser material appeared to be 3-methylquinolizidine, nmr ($CDCl_3$) δ 0.81 (3 *H*, doublet) [lit.[9] bp 72–73° (18 mm)]. Since repeated attempts to separate these components by fractional distillation were not successful, this method for preparation of quinolizidine was abandoned.

The procedure finally used for quinolizidine consisted first in the preparation of 4-quinolizidone by means of Raney nickel hydrogenation of 1,1-dicarbethoxy-3-(2-pyridyl)propane[7] in dioxane solution according to the procedure reported by Bohlman and co-workers.[10] The lactam was then converted in high yield to quinolizidine by the action of lithium aluminum hydride.

1(10)-Dehydroquinolizidine (IV).—This material was prepared by dehydrogenation of quinolizidine with mercuric acetate as reported by Leonard and co-workers.[3] The dehydro base was prepared and kept as its perchlorate salt[3] which, when treated with base, provided the enamine for the experiments described below.

The Site of Hydride Delivery in 1-Carbethoxy-1(10)-dehydroquinolizidine (IX).—1(10)-Dehydroquinolizidinium perchlorate (8.5 g, 37 mmoles) was converted[3] to 1(10)-dehydroquinolizidine (2.85 g, 21.0 mmoles). The latter, contained in 15 ml of dry benzene, was allowed to react with ethyl chloroformate (2.16 g, 20.0 mmoles) at 80° in a nitrogen atmosphere during 5 hr with continuous stirring.[6] The cooled reaction mixture was separated from dehydroquinolizidinium hydrogen chloride by filtration, and the collected solid was washed successively with several small portions of benzene and ether. The wash solutions were combined with the filtrate, and the whole was evaporated to a liquid residue in the steam bath. Distillation gave **1-carbethoxy-1(10)-dehydroquinolizidine** (IX): 2.0 g (50% yield); bp 106° (0.08 mm), ν_{max}^{neat} 1670 (conjugated ester carbonyl) and 1550 cm^{-1} (NC=CC=O).

1-Carbethoxy-1(10)-dehydroquinolizidinium hydrogen chloride was prepared:[11] mp 190–191° (lit.[11] mp 194–195°), $\nu_{max}^{CHCl_3}$ 1680 (conjugated double bond) and 1720 cm^{-1} (conjugated ester carbonyl). The free base was used in each of the following reductions.

1-Carbethoxy-1(10)-dehydroquinolizidine (650 mg, 3.11 mmoles) was dissolved in 4 ml of methanol-*d*, and while the solution was stirred and kept between 5 and 10°, sodium borodeuteride (1.0 g, 30 mmoles) was added in small portions during 2 hr. The reaction mixture was then diluted with 15 ml of deuterium oxide and extracted with ether. Evaporation of the ether left a viscous oil which, upon molecular distillation [100–115° (air bath, 1 mm)], gave **ethyl lupininate-1,10-d_2** (XI): 350 mg (53% yield); ν_{max}^{neat} 2160, 2000 (CD), and 1735 cm^{-1} (saturated ester).

A portion of this dideuterio compound was stirred for 12 hr at room temperature in an ethanolic solution containing sodium ethoxide. The mixture was diluted with water and extracted with ether. The residual oil obtained from evaporation of the

(7) V. Boekelheide and S. Rothchild, *J. Am. Chem. Soc.*, **71**, 879 (1949).

(8) F & M Scientific Corp., Model 500, chromatograph; 16 ft × 0.25 in. copper column packed with Carbowax 20 M, 15% (w/w) on Diatoport.

(9) T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Kartritzky, *J. Chem. Soc.*, 2637 (1962).

(10) F. Bohlmann, N. Ottawa, and R. Keller, *Ann.*, **587**, 162 (1954).

(11) N. J. Leonard, K. Conrow, and R. W. Fulmer, *J. Org. Chem.*, **22**, 1445 (1957).

ether extracts was distilled as before to yield **ethyl lupininate-10-*d*** (X): ν_{max}^{neat} 2160, 2050, and 1735 cm^{-1}.

1-Carbethoxy-1(10)-dehydroquinolizidine was treated with sodium borohydride and the reaction mixture worked up as described above to provide **ethyl lupininate** (XII); bp 130–135° (10 mm) [lit.[12] bp 95–100° (1 mm)], picrate mp 132° dec (lit.[12] mp 137.5–138°), ν_{max}^{neat} 1735 cm^{-1} (saturated ester), with no absorption in the C–D region.

1-Carbethoxy-1(10)-dehydroquinolizidine, as before, was treated with sodium borodeuteride in methanol-*d*, but this time the reaction mixture was hydrolyzed with water. The usual work-up gave **ethyl lupininate-10-*d*** (X). The infrared spectrum (neat) determined from this material showed the same absorption pattern (2150 and 2000 cm^{-1}) in the C–D region as did the ethyl lupininate-d_{10} previously prepared. In addition, the material was treated with sodium ethoxide in ethanol and worked up as before. The infrared spectrum of the recovered ethyl lupininate was unchanged.

(−)- and (+)-Menthyl Chloroformates (Va and Vb).—(−)-Menthol (20.0 g, 0.129 mole) was dissolved in 80 ml of dry toluene containing 8 ml of freshly distilled quinoline. The solution was kept at 0° with gently stirring while phosgene (freed from chlorine by passage through cotton seed oil and then dried by passage through concentrated H_2SO_4) was bubbled through. Phosgene exiting the reaction mixture was absorbed in a 20% NaOH solution. The clear, colorless solution initially absorbed phosgene rapidly, becoming pale yellow and then dark yellow. After a few minutes, however, the gas absorption decreased, and a white, crystalline solid appeared. The passage of phosgene was stopped and, after allowing the reaction mixture to warm to 15–20°, the excess phosgene was pumped from the reaction mixture under gentle suction and absorbed in the alkali solution. The orange, phosgene-free reaction mixture, still maintained near 15°, was washed repeatedly with ice-cold, 4 *N* HCl (four 25-ml portions) and water and then dried over anhydrous Na_2SO_4. Evaporation of the toluene left a liquid residue which, upon fractional distillation, provided **(−)-menthyl chloroformate** (Va): 22.6 g (64.2% yield); bp 97–100° (5 mm) [lit.[13] bp 95° (5 mm)], $[\alpha]^{25}D$ −79.1 ± 0.1° (*c* 3.10, chloroform).

Preparation of the enantiomeric **(+)-menthyl chloroformate** (Vb) was carried out in an identical way, using (+)-menthol.[14] The dextrorotatory isomer, obtained in 88% yield, displayed an identical boiling point and $[\alpha]^{25}D$ +79.8 ± 0.1° (*c* 2.92, chloroform).

(−)- and (+)-1-Menthoxycarbonyl-1(10)-dehydroquinolizidines (IIIa and IIIb).—1(10)-Dehydroquinolizidine (2.02 g, 14.8 mmoles), freshly prepared from 1(10)-dehydroquinolizidinium perchlorate, was dissolved in 15 ml of dry benzene and kept in a nitrogen atmosphere at room temperature with stirring, while a solution of (−)-menthyl chloroformate (Va, 3.27 g, 14.3 mmoles) in 15 ml of dry benzene was added. After the addition was complete, the reaction mixture was heated to 80° where it was maintained and stirred during 5 hr. After the reaction mixture was allowed to cool to room temperature and the precipitated dehydroquinolizidinium hydrogen chloride (1.2 g) was collected by filtration and washed with 10-ml portions of benzene and ether, the washings were combined with the filtrate. The combined solutions were evaporated on the steam bath, and the residue was taken up in ether and filtered once more to remove the last traces of dehydroquinolizidinium hydrogen chloride. Evaporation of the ether from the filtrate left a residual, dark oil which, upon fractional distillation, gave (−)-menthyl chloroformate (1.0 g) and **(−)-1-menthoxycarbonyl-1(10)-dehydroquinolizidine** [IIIa, 1.04 g, 42% yield, bp 160° (0.08 mm)] as a highly viscous, pale yellow oil: $[\alpha]^{28}D$ −61.1 ± 0.2° (*c* 2.91, ethanol), ν_{max}^{neat} 1550 (conjugated double bond) and 1650 cm^{-1} (conjugated ester carbonyl).

The product was further characterized as its picrate salt, mp 131° dec, recrystallized from ethanol.

Anal. Calcd for $C_{26}H_{36}N_4O_9$: C, 56.90; H, 6.62; N, 10.22. Found: C, 57.18; H, 6.57; N, 10.21.

In the same way, **(+)-1-menthoxycarbonyl-1,(10)-dehydroquinolizidine** [IIIb, $[\alpha]^{27}D$ +64.5 ± 0.5° (*c* 3.10, ethanol)] was prepared using (+)-menthyl chloroformate (Vb).

Sodium Borohydride Reduction of (−)- and (+)-1-Menthoxycarbonyl-1(10)-dehydroquinolizidines (IIIa and IIIb).—(−)-1-Menthoxycarbonyl-1(10)-dehydroquinolizidine (630 mg, 1.97 mmoles), dissolved in 10 ml of dry methanol and kept at 0–5°, was treated portionwise with sodium borohydride (300 mg, 9.38 mmoles) during 2 hr. After addition was complete, the reaction mixture was stirred for an additional 30-min period at the same temperature. After 50 ml of water was added and the hydrolyzate was extracted with ether, the combined ether extracts were dried and evaporated to a liquid residue which was molecularly distilled [154–164° (air bath, 0.08 mm)] to yield **(−)-1-menthoxycarbonylquinolizidine** (VIIIa), $[\alpha]^{27}D$ −53.7 ± 0.4° (*c* 3.51, ethanol).

Anal. Calcd for $C_{20}H_{35}NO_2$: C, 74.71; H, 10.97; N, 4.36. Found: C, 74.91; H, 10.95; N, 4.58.

In the same way (+)-1-menthoxycarbonyl-1(10)-dehydroquinolizidine (IIIb) was reduced to **(+)-1-menthoxycarbonylquinolizidine** (VIIb), $[\alpha]^{26}D$ +52.4 ± 0.2° (*c* 4.01, ethanol).

The levorotatory product was carefully chromatographed on a thin layer silica gel system and through a 16 ft × 0.25 in. vapor phase column packed with 15% (w/w) Carbowax 20 M on Diatoport under various conditions of temperature and helium flow rate in attempts to detect the presence of diastereoisomers. In all attempts only one component could be observed.

Reduction of (−)- and (+)-1-Menthoxycarbonylquinolizidines (VIIa and VIIIb) to (+)- and (−)-Lupines (Ia and Ia).—A solution of (−)-1-menthoxycarbonylquinolizidine (VIIf, 580 mg, 1.82 mmoles) in 30 ml of dry ether was added dropwise to a stirred suspension of lithium aluminum hydride (600 mg, 15.8 mmoles) in 10 ml of dry ether at room temperature. After the reaction mixture was stirred for 1 hr, the excess lithium aluminum hydride was destroyed by addition of moist ether and then diluted with water. The hydrolyzate was phase separated, and the aqueous phase was extracted with ether. The ether extracts were combined with the original ethereal phase, dried, and concentrated to a final volume of 20 ml. The ethereal concentrate was saturated with hydrogen chloride. The resulting precipitate was collected by filtration, washed with dry ether, and dissolved in 5 ml of water. Addition of sodium carbonate to the aqueous solution liberated the basic product which was then extracted into ether. Evaporation of the ether left a dark, viscous oil which was molecularly distilled to give a colorless oil which crystallized, mp 54–58°. Recrystallization from hexane provided **(+)-lupinine** (Ia): 65 mg, mp 57–58°, $[\alpha]^{26}D$ +2.10 ± 0.4° (*c* 6.10, ethanol).

Evidently lupinine forms a racemic compound since synthetic, racemic lupinine has been reported with mp 59°,[2] while optically active natural lupinine has mp 70–71°.[4] Epilupinine (VIII), racemic or active has a melting point near 81°.[4] In the present work no evidence for the presence of epilupinine could be obtained. Examination of the reaction product by means of thin layer chromatography, under conditions which were previously shown to separate lupinine from epilupinine, did not reveal the presence of epilupinine in the reaction product. In addition, an admixture of 90% racemic lupinine and 10% natural (−)-lupinine was observed to melt at 57–58°, the same mp displayed by the reaction product.[15]

Lithium aluminum hydride reduction of (+)-1-menthoxycarbonylquinolizidine (VIIb), under the same conditions and work-up as above, provided **(−)-lupinine** (Ib), mp 57–58°, $[\alpha]^{26}D$ −2.02 ± 0.1° (*c* 5.10, ethanol).

Reduction of (−)-1-Menthoxycarbonyl-1(10)-dehydroquinolizidinium Hydrogen Chloride (XV).—(−)-1-Menthoxycarbonyl-1(10)-dehydroquinolizidinine was converted to its hydrochloride salt by saturating an ethereal solution of the former with hydrogen chloride. The precipitated salt was collected and dried. A sample (2.00 g, 5.62 mmoles) was dissolved in 25 ml of dry methanol and treated with sodium borohydride in the usual way to yield the saturated ester, 1-menthoxycarbonylquinolizidine (VII, 1.66 g), which was directly treated with lithium aluminum hydride in ether solution as in the previous reductions. The

(12) V. Boekelheide, W. J. Linn, P. O'Grady, and M. Lamborg, *J. Am. Chem. Soc.*, **75**, 3243 (1953).

(13) Preparation of menthyl chloroformate has been cited [A. N. Kost, *Uch. Zap. Mosk. Gos. Univ.*, **131**, 39 (1950)], but no procedural details were given in that report.

(14) (+)-Menthol was obtained from resolution of racemic menthol according to the experimental procedures cited by A. W. Ingersoll [*Org. Reactions*, **2**, 398 (1944)].

(15) The specific rotation of the present synthetic material indicated it to be a 55:45 mixture of (+)/(−)-lupinine, or approximately 10% optical yield since natural lupinine has $[\alpha]D$ −20.9°.[4]

same reaction work-up provided (+)-**lupine** (Ia): 170 mg, mp 57–58°, $[\alpha]^{26}D$ +1.43 ± 0.1° (*c* 14.1, ethanol).

Registry No.—VI, 493-10-7; IX, 7635-52-1; XI, 7688-06-4; X, 7695-29-6; Va, 7635-53-2; Vb, 7635-54-3; IIIa, 7635-55-4; IIIa picrate, 7635-56-5; IIIb, 7635-57-6; VIIa, 7635-58-7; VIIb, 7635-59-8; Ia, 7635-60-1; Ib, 3000-87-1; XV, 7635-62-3.

Acknowledgments.—We are pleased to acknowledge our thanks to the National Institute of Mental Health for their generous support of this work.

Synthesis of (±)-Cryptowoline Iodide

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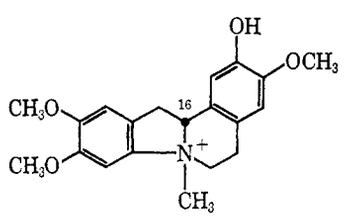
The synthesis of (±)-cryptowoline iodide by an unequivocal route confirms the previously assigned structure, 2-hydroxy-3-methoxy-8-methyl-11,12-methylenedioxy-6,7,15,16-tetrahydro[*b*,*g*]pyrrocolinium iodide.

Cryptowoline (XIII), one of the principal alkaloids of *Cryptocarya bowiei* (Hook) Druce, indigenous to southern Queensland, Australia, was isolated as its sparingly soluble iodide and characterized over a decade ago.[2] Both XIII and the related alkaloid cryptaustoline (Ia) were shown to be ethers of dehydrolaudanosoline, and a synthesis was reported of O-methylcryptaustoline[3] identical with the O-methylation product of Ia. Oxidation of *d*-laudanosine in the manner described by Robinson and Sugasawa[4] and by Schöpf and Thierfelder[5] was used to obtain the 2,3,11,12-tetramethoxy-8-methyl-6,7,15,16-tetrahydrodibenzo[*b*,*g*]-pyrrocolinium iodide (O-methylcryptaustoline iodide) which corresponds to natural cryptaustoline in having the correct configuration around C_{16}.



Ia

In the course of this study, we undertook the total synthesis of cryptowoline iodide[6] (XIII) from substituted aromatic intermediates which would lead ultimately to proper substituents in the A and D rings in XIII. The two key intermediates in this approach to XIII were 3-methoxy-4-benzyloxy-β-phenethylamine (II) and 6-bromohomopiperonylic acid (VI). In our initial attempts to obtain I, the β-nitrostyrene precursor of II, O-benzylvanillin,[7] was treated with nitromethane under the amine-catalyzed conditions described by Tomita and Watanabe.[8] In our hands, this condensation gave only polymeric compounds and none of the desired β-nitrostyrene (I). The same condensation reaction, when carried out in the presence of alcoholic potassium hydroxide, afforded I in good yield. Reduction of I with lithium aluminum hydride, in the usual manner, gave the desired 3-methoxy-4-benzyloxy-β-phenethylamine (II). Piperonyl alcohol (III) served as a starting material for the synthesis of 6-bromohomopiperonylic acid (VI).[9] Treatment of III with thionyl chloride gave crude 3,4-methylenedioxybenzyl chloride which was converted to homopiperonitrile in 90% yield by warming at 35–40° with potassium cyanide in dimethyl sulfoxide solution.[10] Esterification of IV followed by saponification gave the desired homo acid (V) which was, in turn, brominated smoothly to VI.

The acid chloride of VI was converted into N-(3-methoxy-4-benzyloxy-β-phenethyl)-6′-bromohomopiperonylamide (VII) by the action of excess 3-methoxy-4-benzyloxy-β-phenethylamine in ether solution. A Bischler–Napieralski cyclization of amide VII, effected by phosphoryl chloride in boiling toluene, gave 1-(6′-bromopiperonyl)-6-methoxy-7-benzyloxy-3,4-dihydroisoquinoline (VIII) in 80% yield. Hydrogenation of a methanolic solution of VIII, containing slightly more than 1 equiv of concentrated hydrochloric acid, over a platinum oxide catalyst afforded (±)-1-(6′-piperonyl)-6-methoxy-7-benzyloxy-1,2,3,4-tetrahydroisoquinoline (IX).

Since our synthesis was aimed originally at obtaining (−)-cryptowoline iodide, it was thought that the resolution of the tetrahydroisoquinoline base IX could be carried out to give the pair of enantimorphs, each of which would then be carried through intermediates IX–XIII; one of these isomers of IX would ultimately result in a correct configuration at C_{16} in structure XIII corresponding to (−)-cryptowoline. Reaction of (±)-IX with sufficient O,O′-dibenzoyl-L-tartaric acid to form an acid salt of the base proved to be an excellent method for separating the required enantimorphs; the (+) base O,O′-dibenzoyl-L-tartrate was nearly insoluble in ethyl acetate whereas the corresponding salt of the (−) base was extremely soluble in this solvent. The pure (+) and (−) enantimorphs of IX were regenerated by treating the purified salts with alkali.

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(6) Following the ring-numbering system shown for Ia, this alkaloid is systematically named as 2-hydroxy-3-methoxy-11,12-methylenedioxy-6,7,15,16-tetrahydrodibenzo[*b*,*g*]pyrrocolinium iodide.

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