since amines giving two spots in one acidic solvent (*i.e.*, *n*-butanol–acetic acid–water) give only one spot in another (*i.e.*, water–hydrochloric acid–phenol). Moreover, amines which appeared to give six or more spots when chromatographed from freshly prepared solutions in 10 *N* hydrochloric acid on cellulose paper (7) gave only two spots when chromatographed from the same freshly prepared solution on cellulose thin layer. In the former, a gradual decrease, while in the latter, a gradual increase in the number of the spots with the age of the solution was observed.

It is therefore concluded that the formation of two amine spots, when cellulose thin layers are used, results from the following factors: (*a*) a continuity of adsorption forces along the direction of the mobile solvent on cellulose thin layers (9, 10), (*b*) a combination of adsorption and partition forces, and (*c*) the presence of the carboxyl groups in the prepared cellulose. That the presence of the carboxyl groups in the prepared cellulose is leading to the formation of double spots, has been previously discussed (10) and therefore further discussion here is unnecessary.

This investigation shows that the presence of more than one spot in cellulose chromatograms, using extracted biological material, does not necessarily indicate that two or more amines are present.

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Modified Synthesis of *dl-N*-Norarmepavine and *dl*-Armepavine

By JOSEPH SAM and A. J. BEJ

The synthesis of *dl-N*-norarmepavine and *dl*-armepavine, utilizing the carboethoxy protecting group, is described.

THE POTENTIAL of *dl*-1-(4-hydroxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (V*a*) as an intermediate to medicinal agents prompted an investigation of its synthesis. The levorotatory base (V*a*) was first isolated by Kupchan and coworkers (1, 2) from *Nelumbo lutea* and named (−)-*N*-norarmepavine. The alkaloid subsequently was isolated by Tomita, Yang, and Lu (3), and by Yang (4).

A total synthesis of V*a* *via* the Bischler-Napieralski reaction has been reported by Yamaguchi and Nakano (5). The benzyl group was utilized for the protection of the phenolic hydroxyl group. This report describes the use of the carboethoxy protecting group in the preparation of V*a* and V*b*.

The requisite amide (III*b*) for the Bischler-Napieralski reaction was prepared either from III*a* or by the condensation of I with the acid chloride (6) of II*b*. The cyclization of III*b* to IV*a* was accomplished with phosphorus oxychloride. The low pressure reduction of IV*a* followed by hydrolysis gave V*a*. Alternately, V*a* was prepared by the hydrolysis of IV*a* to IV*b*, followed by sodium borohydride reduction. It was observed also that sodium borohydride converts IV*a* directly to V*a*. Treatment of V*a* with formic acid and formaldehyde provided *dl*-armepavine (V*b*). Since V*a* was converted to *dl*-armepavine (V*b*), as described above, this sequence also comprises a total synthesis of the alkaloid (Scheme I.)

The nuclear magnetic resonance (NMR) spectrum of V*a* in deuteriochloroform showed six aromatic protons (τ = 3.0–3.4), two labile protons (τ = 5.4, by D_2O exchange), one tertiary proton (quadruplet centered at τ 5.85), and six methoxyl protons (broad doublet centered at τ 7.05), which is in good agreement with the reported NMR spectrum of (−)-*N*-norarmepavine (2).

Sufficient work has not been done to make a critical comparison of the various methods of protecting the phenolic hydroxyl group in the preparation of *dl-N*-norarmepavine. The use of sodium borohydride in the reduction of IV*a* with attendant hydrolysis of the carboethoxy group, however, provides a means of removing the protecting group under alkaline conditions.

EXPERIMENTAL[1]

N-β-(3,4-Dimethoxyphenethyl)-4-hydroxyphenylacetamide (IIIa)—A mixture of 3.6 Gm. (0.02 mole) of homoveratrylamine, 3.0 Gm. (0.02 mole) of *p*-hydroxyphenylacetic acid, 10 ml. of dry decalin, and 10 ml. of tetralin was refluxed at 180–185° for 8 hr. The solvent was decanted from the semisolid; the last traces of solvent were removed by steam distillation. The residual solid was washed successively with 10% sodium bicarbonate, water,

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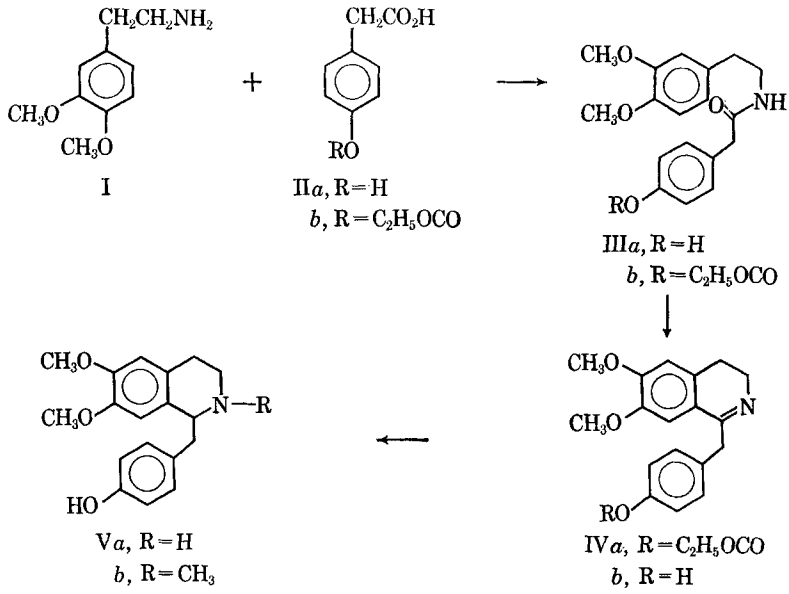
[1] Melting points were taken in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus and are corrected. Infrared spectra were determined on a Perkin-Elmer model 137 G Infracord spectrophotometer. The NMR spectrum of *dl-N* norarmepavine (V*a*) was obtained by means of the Varian A-60A spectrometer using tetramethylsilane (TMS) as the internal standard and deuteriochloroform as the solvent. The shifts were measured on the τ-scale relative to the internal standard TMS (τ 10.0). Assignment of protons in a certain area is based on correct integral information from the NMR spectrum.



Scheme I

10% hydrochloric acid, and water. The recrystallization of the residual material from ethanol gave 5.0 Gm. (81%) of an amorphous solid, m.p. 153–155°. The infrared spectrum possessed an absorption peak at 6.1 μ characteristic of an amide function. The methoxy analog was prepared in the usual manner and recrystallized from ethanol, m.p. 123–124°. [Lit. (7) m.p. 123–125°).]

N-β-(3,4-Dimethoxyphenethyl)-4-ethoxycarbonyloxyphenylacetamide (IIIb)—*Method A*—A solution of 3.1 Gm. (0.01 mole) of *N*-β-(3,4-dimethoxyphenethyl)-4-hydroxyphenylacetamide (III*a*) in 45 ml. of 5% potassium hydroxide was treated slowly, with shaking, with 1.1 Gm. (0.01 mole) of ethyl chloroformate. The mixture was shaken for 15 min. and then filtered to remove the solid product. The filtrate again was treated with 1.1 Gm. (0.01 mole) of ethyl chloroformate as above. The combined solid product was washed with a copious amount of water and then recrystallized from a mixture of benzene and petroleum ether (30–60°). There was obtained 3 Gm. (81%) of feathery needles, m.p. 95–96°. The infrared spectrum possessed two carbonyl absorption peaks at 5.8 μ and 6.1 μ, characteristic of esters and amides, respectively.

Anal.—Calcd. for $C_{21}H_{25}NO_5$: C, 65.1; H, 6.5; N, 3.6. Found: C, 65.3; H, 6.5; N, 3.8.

Method B—A solution of 4-ethoxycarbonyloxyphenylacetyl chloride (6) [from 5 Gm. (0.022 mole) of the acid] in 15 ml. of tetraethylene glycol dimethyl ether was added dropwise at approximately 16° to a stirred mixture of 3.6 Gm. (0.02 mole) of homoveratrylamine, a solution of 2 Gm. of sodium hydroxide in 6 ml. of water, and 15 ml. of tetraethylene glycol dimethyl ether. During the mixing the temperature rose to about 30°. After the addition was complete (5 min.), the reaction mixture was poured into 100 ml. of cold water and adjusted to pH 10. The crude product was removed by filtration and washed with water. The recrystallization of the crude material from a mixture of benzene and petroleum ether (30–60°) gave 2.5 Gm. (31%) of product, m.p. 95–96°. A mixed melting point with the product obtained from method *A* showed no depression.

1-(4-Ethoxycarbonyloxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline Hydrochloride (IVa)—The method described by Finkelstein (6) was followed using 2.6 Gm. (0.007 mole) of *N*-β-(3,4-dimethoxyphenethyl)-4-ethoxycarbonyloxyphenylacetamide (III*b*), 30 ml. of dry toluene, and 1.5 Gm. (0.01 mole) of phosphorus oxychloride. The toluene was decanted from the reaction mixture and the unreacted phosphorus oxychloride was distilled under reduced pressure. The residual solid was recrystallized from ethanol to give 2.2 Gm. (76%) of product, m.p. 210–211°.

Anal.—Calcd. for $C_{21}H_{24}ClNO_5$: C, 62.1; H, 6.0; Cl, 8.7; N, 3.5. Found: C, 62.1; H, 6.1; Cl, 8.9 N, 3.4.

1-(4-Hydroxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline Hydrochloride (IVb)—Six grams (0.015 mole) of 1-(4-ethoxycarbonyloxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride (IV*a*) was heated on a steam bath with 70 ml. of 20% hydrochloric acid until evolution of carbon dioxide ceased (90 min.). The solvent was distilled under reduced pressure. The residual semisolid was treated with 200 ml. of dry benzene and distilled to remove the water. The residual solid (m.p. 195–200°, 4.7 Gm., 94%) was triturated with 30 ml. of acetone and recrystallized from methanol, m.p. 202.5–204°.

Anal.—Calcd. for $C_{18}H_{20}ClNO_3$: Cl, 10.6; N, 4.2. Found: Cl, 10.1; N, 3.9.

dl-1-(4-Hydroxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (dl-N-Norarmepavine) (Va)—*Method A*—A solution of 2.0 Gm. (0.005 mole) of 1-(4-ethoxycarbonyloxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride (IV*a*) in 50 ml. methanol was treated with 50 mg. of PtO_2 and hydrogenated at 25° for 1.7 hr. The product was isolated in the usual manner. The crude hydrogenation product was treated with 5 ml. of 15% hydrochloric acid and heated on a steam bath for 20 min. The acid solution was cooled to room

temperature and refrigerated for 10 hr. The hydrochloride (0.8 Gm., 50%, m.p. 194–196°) was removed by filtration and recrystallized twice from a mixture of methanol and ethyl acetate, m.p. 194–196°.

Anal.—Calcd. for $C_{18}H_{22}ClNO_3$: C, 64.4; H, 6.6; Cl, 10.5; N, 4.1. Found: C, 64.2; H, 6.6; Cl, 10.5; N, 4.3.

The free base was prepared in the usual manner and recrystallized from a mixture of ethyl acetate and *n*-hexane, m.p. 99–101°, softens around 94°. [Lit. (5) m.p. 95–96°.] The oxalate was prepared in the usual manner and recrystallized from methanol, m.p. 214–215°. [Lit. (5) m.p. 202–204°.]

Method B—A mixture of 1.6 Gm. (0.005 mole of 1 - (4 - hydroxybenzyl) - 6,7 - dimethoxy - 3,4 - dihydroisoquinoline hydrochloride (IV*b*), 50 ml. of methanol, and 3.5 Gm. of sodium borohydride was stirred for 30 min. The reaction mixture was treated with 2 ml. of water and refluxed with stirring on a steam bath for 1.7 hr. Most of the methanol was distilled under reduced pressure. The residue was poured onto a mixture of crushed ice and water (250 Gm.). The mixture was adjusted to pH 8 and extracted with three 50-ml. portions of ether. The ether extract was dried over anhydrous sodium sulfate. The evaporation of the ether left 1 Gm. (62%) of an oil. The hydrochoride was prepared in the usual manner and recrystallized from a mixture of methanol and ethyl acetate, m.p. 194–196° A mixed melting point with a sample prepared by method *A* showed no depression. The oil was crystallized from a mixture of ethyl acetate and hexane or from acetone to give 0.5 Gm. (31%) of an amorphous solid, m.p. 99–101°, softens around 94°. The infrared spectrum in chloroform of this sample was identical with the infrared spectrum of the sample obtained by method *A*. The oxalate was prepared in the usual manner and recrystallized from methanol, m.p. 214–215°.

Method C—A solution of 4.0 Gm. (0.01 mole) of 1 - (4 - ethoxycarbonyloxybenzyl) - 6,7 - dimethoxy-3,4-dihydroisoquinoline hydrochloride (IV*a*) in 100 ml. of methanol was reduced with 10 Gm. of sodium borohydride and worked up as described in method *B*. The free base (1 Gm., 34%), the hydrochloride, and the oxalate were identical (mixed melting point showed no depression) with the samples obtained by methods *A* and *B*.

dl-Armepavine (Vb)—A mixture of 0.5 Gm. (0.0017 mole) of *dl*-1-(4-hydroxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (V*a*), 6 ml. of 98% formic acid, and 6 ml. of 40% formalin was heated under reflux for 6 hr. The mixture was diluted with water, adjusted to pH 9, and extracted three times with 50-ml. portions of chloroform. The chloroform extract was washed with water and dried over anhydrous sodium sulfate. The distillation of the chloroform under reduced pressure left an oil which was chromatographed on a column of Woelm neutral alumina (activity I) with acetone as the eluent. From the acetone eluent was obtained an oil which was crystallized from a mixture of ethyl acetate and hexane to yield 0.15 Gm. (29%) of *dl*-armepavine, m.p. 158.5–160.5°. [Lit. (8, 9) m.p. 159–161°.]

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Ursolic Acid in *Retanilla ephedra*

By MARIO SILVA

Ursolic acid was isolated from *Retanilla ephedra*.

In connection with a study on sapogenins and alkaloids (1–8) of certain typical Chilean species now under way in this laboratory, it appeared of interest to study *Retanilla ephedra* (Vent.) Brongn., Chilean *Rhamnaceae*, in order to study the sapogenin described by Moyano (9) and to elucidate the presence or absence of alkaloids.

This is a chemical study of the petroleum ether and alcohol-soluble fractions of dried and pulverized plant. The petroleum ether-soluble fraction yielded two products, an alcohol and an acidic compound. The defatted plant material was dried and then extracted with alcohol. This extract gave a water-soluble glycosidic fraction. Acid hydrolysis of this material yielded an acidic sapogenin, identical with the acidic compound isolated from the petroleum ether fraction. This acid was identified as ursolic acid and further characterized through its acetate, methyl ester, and methyl ester acetate. The isolation of an alkaloid present in this water-soluble fraction is now in progress.

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EXPERIMENTAL[1]

Petroleum Ether Extract—Stems of *R. ephedra* collected in February 1962 near Buchupureo

[1] Melting points (uncorrected) were determined on a Kofler block. Rotations wereme asured at 20°. The ultraviolet spectrum was recorded in solution in absolute ethanol on a SP 700 spectrophotometer. Infrared spectra were recorded on a Perkin Elmer 137 spectrophotometer.