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.

(Maule) were dried at 80–90°. A 1550-Gm. quantity of dried and ground plant was extracted in a Soxhlet extractor with petroleum ether (b.p. 65–75°) to exhaustion. This dark solution was concentrated to yield 50 Gm. of a dark green product. This product was refluxed for 1 hr. in a 5% sodium hydroxide ethanolic solution. The neutral product was found to be a polymethylenic alcohol of low melting point. The acidic fraction yielded, after several recrystallizations, 100 mg. of a compound, m.p. 273–275°; $[\alpha]_D^{20°}$ + 61° (pyridine c 0.45).

Alcoholic Extract—The defatted plant material was dried and the ethanol-soluble constituents were extracted. This dark solution was concentrated to yield 415 Gm. of a water-soluble product. This product was treated with 2.5 *N* ethanolic hydrochloric acid. The mixture was then refluxed for 5 hr. and poured into ice water. After 48 hr. the precipitate was collected on a filter and washed with water, yielding 215 Gm. of a light green mass. The crude ursolic acid was partially purified by continuous extraction, first with petroleum ether (b.p. 65–75°), then with a mixture of petroleum ether–benzene and, finally, with benzene. After recrystallizations of the product extracted with the mixture petroleum ether–benzene and benzene, 450 mg. of an acid, m.p. 267–279°, was obtained.

Ursolic Acid—Several recrystallizations of the previously obtained compound yielded ursolic acid, m.p. 281°; $[\alpha]_D^{20°}$ +61° (pyridine c 0.6), $\nu_{max.}^{KCl}$ 3350 and 1695 cm.$^{-1}$.

Ursolic Acid Acetate—The pure compound was obtained as needles after crystallization from methanol–chloroform, m.p. 281°.

Ursolic Acid Methyl Ester—This ester was prepared by diazomethane treatment of the acid in ethereal solution, crystallized from methanol–chloroform as colorless crystals, m.p. 170°; $\lambda_{max.}^{EtOH}$ 206 mμ ε 5000, $\nu_{max.}^{CHCl_3}$ 3410, 1754, and 1642 cm.$^{-1}$.

The melting point of this compound was undepressed upon admixture with an authentic specimen, m.p. 171°, and was found to be identical with the methyl ester of the acidic compound, m.p. 273–275°, previously isolated from the petroleum ether extract.

Ursolic Acid Methyl Ester Acetate—It was obtained as needles after crystallization from methanol–chloroform, m.p. 243–244°; $[\alpha]_D^{20°}$ +60° (chloroform c 0.48).

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Synthesis and Basic Pharmacology of *N*-Substituted and *N,N'*-Disubstituted Allyl Barbiturates

By M. H. WEINSWIG, A. M. BURKMAN*, W. D. JONES, and E. J. ROWE

***N*-Substituted and *N,N'*-disubstituted allyl derivatives of barbital, phenobarbital, hexobarbital, and diallylbarbital have been synthesized by the use of a strongly basic anion-exchange resin. The barbiturate is first absorbed on the resin and the resin then agitated mechanically with an ethanol solution of benzyl chloride. None of the allyl barbiturates approached phenobarbital in terms of pharmacological potency.**

In previous reports (1, 2) a method was described for the synthesis of benzyl ethers of a variety of phenols and of 5,5-disubstituted barbiturates by the use of a strongly basic anion-exchange resin. The method involved the reaction of the phenolate or the barbiturate form of the resin with benzyl chloride. The synthesis of the *N*-allyl and the *N,N'*-diallyl barbiturate derivatives seemed feasible, using this method, since the allyl and the benzyl halides are believed equally reactive chemically. This report presents an analogous method for the synthesis of *N*-allyl and *N,N'*-diallyl derivatives of four 5,5-disubstituted barbituric acids (phenobarbital, barbital, hexobarbital, and diallylbarbital) and the synthesis of 5,5-diallylbarbituric acid.

SYNTHESIS

The synthesis of these derivatives involved the reaction of the barbiturate form of a strongly basic anion-exchange resin with allyl bromide. The resin employed was a polystyrene polymer containing reactive quaternary ammonium groups. Proceeding at room temperature, a mixture of *N*-allyl and *N,N'*-diallyl derivatives was obtained from the reaction. Separation of the derivatives was effected by taking advantage of the solubility of the *N*-allyl derivative in dilute alkali. Table I presents the analytical data for allyl derivatives of barbituric acid, phenobarbital (5-ethyl-5-phenyl barbituric acid), barbital (5,5-diethyl barbituric acid), and hexobarbital (*N*-methyl-5-methyl-5-cyclohexenyl barbituric acid) prepared by the use of a strongly basic anion-exchange resin. The *N,N'*-diallyl derivative is the main product when an equivalency of the resin in the OH form is used with the barbiturate form and the quantity of the allyl bromide is doubled plus 10% excess.

Resin Preparation—Synthetic ion-exchange resin made from styrene-divinylbenzene copolymer[1] supplied commercially in the chloride form (20–50

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[1] Dowex IX4, Dow Chemical Co., Midland, Mich.