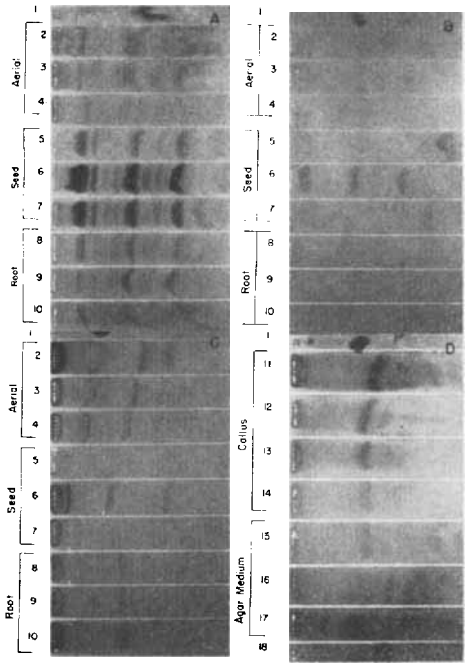

Fig. 2.—Thin-layer chromatograms of morning glory seeds, plants, and tissue cultures. Key: A, plants and seeds: alkaline chloroform extract (fraction A); B, plants and seeds: pH 6.8 chloroform extract (fraction B); C, plants and seeds: pH 6.8 aqueous extract (fraction C); D, tissue culture: alkaline chloroform extract (fraction A). Number code: clymoclavine, 1; pearly gates, 2, 5, 8, 11, 15; heavenly blue, 3, 6, 9, 12, 16; flying saucer, 4, 7, 10, 13, 17; *Rivea corymbosa*, 14; agroclavine, 18. Amounts applied: A, aerial 100 μl.; seed, 50 μl.; root, 150 μl.; B, C, and D, 100 μl. Adsorbent: Adsorbosil-1 (Applied Science Lab., Inc., State College, Pa.). Solvent system: chloroform–methanol (17:3). Spray reagent: PDAB–sodium nitrite.

(fraction B) upon adjustment of the alkaline aqueous solution to pH 6.8 (Table I and Fig. 2, B). The remaining aqueous solution (fraction C) might also contain alkaloids (Fig. 2, C), or indole-type compounds.

Only trace amounts of alkaloids were detected spectrophotometrically in flying saucer, pearly gates, and *Rivea* callus and in flying saucer and pearly gates agar growth medium. No alkaloids were detected spectrophotometrically in heavenly blue tissue cultures (Table I). Although callus tissue cultures more consistently contained alkaloids than their respective medium, the medium extract occasionally gave a more positive and complex pattern than the callus extract on thin-layer plates (Fig. 2, D). Further work is in progress to determine if *Argyreia* and *Ipomoea* suspension cultures produce alkaloids.

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Synthetic Approach to Dihydrokavain

By EDWARD E. SMISSMAN, A. NELSON VOLDENG, and JOHN F. MCCARTHY

The preparation of δ-phenylethyl-δ-valerolactone (XII) *via* the alkylation of dihydroresorcinol, followed by a reverse Claisen reaction, and the attempted preparation of dihydrokavain (I), by a modification of this method, are discussed.

FOR CENTURIES the natives of the South Pacific islands have employed the root and rhizome of the kava-kava shrub (*Piper methysticum* Forst.), also known as "ava," "kava," "yangona," and "hoi," to prepare an intoxicating beverage called kava which is consumed at various rituals. The kava beverage, if consumed in sufficient quantity, produces a state of euphoria, followed shortly by muscular relaxation, loss of control of the extremities, and finally a period of dreamless sleep which may last 10 hr. or more. Upon awakening there are apparently no undesirable effects (1–3).

While kava-kava contains a number of components having the pyrone and dihydropyrone

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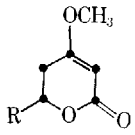
nucleus, only two, dihydrokavain (I) and dihydromethysticin (II), have been shown to produce the characteristic soporific effect (4–6).



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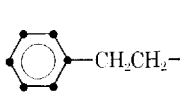
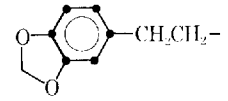
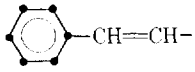


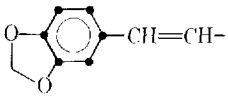
Dihydrokavain (I)



Dihydromethysticin (II)



Kavain (III)



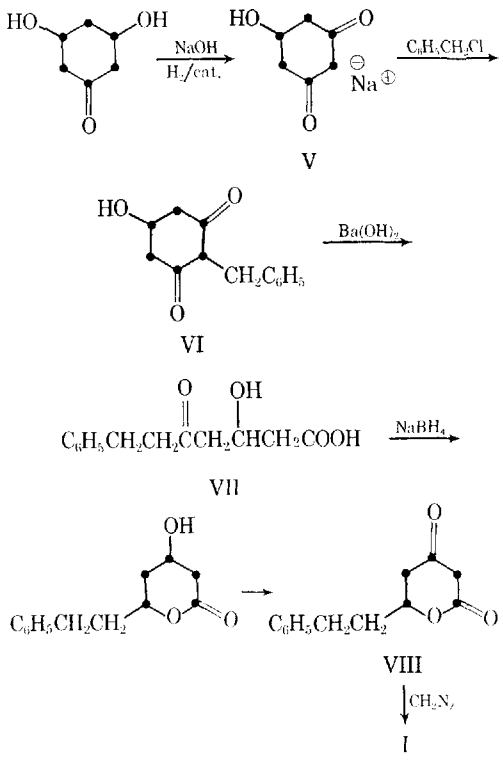
Methysticin (IV)

Dihydrokavain (I) has been synthesized; however, the reaction sequence is lengthy and the yield is low (7). The present source of dihydrokavin (I) and dihydromethysticin (II) is either by isolation from the kava-kava plant or by reduction of kavain (III) and methysticin (IV), respectively.

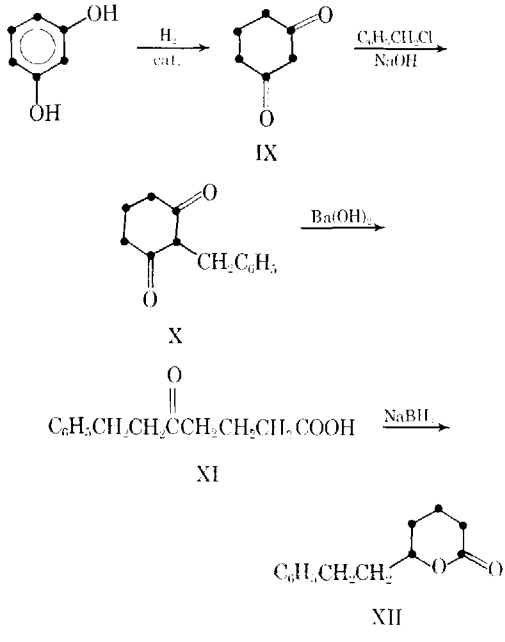
The unique chemistry and pharmacology associated with these dihydropyrones prompted this investigation. It was envisioned that the desired lactones could be prepared by the scheme shown in Scheme I.

Reduction of phloroglucinol followed by alkylation of the monosodium salt (V) would yield the alkylated dione (VI). A reverse Claisen reaction would afford the keto-acid (VII), which in turn could be lactonized and oxidized to the keto-lactone (VIII). Treatment with diazomethane would then afford dihydrokavain (I). Dihydromethysticin (II) and other analogs could be prepared in an analogous manner, using the appropriately substituted benzyl chloride.

Before investigating this approach, it was decided to use resorcinol as a model starting compound (Scheme II). Reduction of resorcinol with Raney nickel catalyst afforded dihydroresorcinol (XI) which was alkylated with benzyl chloride, giving rise to 2-benzylcyclohexane-1,3-dione (X). A reverse Claisen reaction using barium hydroxide as the base, followed by reductive lactonization of the keto-acid (XI) gave rise to the lactone (XII).



Scheme I

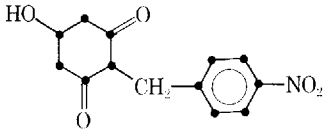


Scheme II

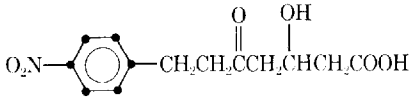
Applying the same sequence of reactions (Scheme I) to phloroglucinol afforded much lower yields of the corresponding compounds. Reduction of phloroglucinol with Raney nickel catalyst yielded monosodiodihydrophloroglucinol

(V) in a 35% yield. When 5% rhodium on alumina was used as the catalyst, the monosodium salt (V) was obtained in 95% yield. Alkylation of the salt (V) with benzyl chloride gave rise to 2-benzyl-5-hydroxycyclohexane-1,3-dione (VI) in 15% yield. Attempts to increase this yield by the use of benzyl iodide, bromide, and tosylate, or by employing various solvents and temperatures were unsuccessful. Formation of the heptanoic acid (VII) from the dione (VI) by means of a reverse Claisen reaction was also unsuccessful. Various temperatures and bases were employed, but the keto-acid was not produced.

The use of a modified procedure of Kornblum (8) in which *p*-nitrobenzyl chloride is used as the alkylating agent, afforded a 30% yield of the nitro dione (XIII). Attempts to open the dione ring (XIII) by means of a reverse Claisen reaction did not afford the keto-acid (XIV).



XIII



XIV

EXPERIMENTAL

Dihydroresorcinol (IX). This material, m.p. 103–104°, was prepared in 90% yield by the procedure of Thompson (9). (Lit. m.p. 103–104°.)

2-Benzylcyclohexane-1,3-dione (X).—This substance, m.p. 184°, was prepared in 70% yield by the procedure of Stetter and Dierichs (10). (Lit. m.p. 184°.)

5-Oxo-7-phenylheptanoic Acid (XI).—This material, m.p. 58°, was prepared in 78% yield by the procedure of Stetter and Dierichs (10). (Lit. m.p. 58°.)

δ-Phenylethyl-δ-valerolacetone (XII).—The procedure for the preparation of this material was patterned after that of Chaikin and Brown (11). Five per cent aqueous sodium hydroxide was added dropwise to 4.3 Gm. (0.019 mole) of 5-oxo-7-phenylheptanoic acid (XI), which was suspended in water, to phenolphthalein end point. This solution was added over a period of 15 min. to 0.23 Gm. of sodium borohydride (0.006 mole) dissolved in 10 ml. of water. The reaction was stirred during the addition and for 1 hr. after the addition was complete. The solution was then acidified to Congo red with 10% hydrochloric acid and stirred for 15 min. at room temperature. The cloudy mixture was then extracted with three 50-ml. portions of ether, the ether dried over anhydrous magnesium sulfate, and evaporated. The resulting oil was distilled under reduced pressure to give 2.8 Gm. (70%) of the lactone, XII, b.p. 140–143° (0.05 mm.); n^{25} 1.5320. The infrared spectrum (liquid film) exhibited strong absorption at 6.75 μ (C=O).

Anal.—Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.64; H, 8.38.

Monosodiodihydrophloroglucinol (V).—The procedure for the reduction of phloroglucinol was patterned after a method for the reduction of resorcinol reported by Esch and Schaeffer (12). To a solution of 15 Gm. (0.376 mole) of sodium hydroxide in 100 ml. of water was added 61.0 Gm. (0.376 mole) of phloroglucinol dihydrate and the total volume of the solution was made 200 ml. This solution was placed in a 500-ml. hydrogenation bottle, 4.7 Gm. of 5% rhodium on alumina (Engelhard Industries, Inc.) was added, and the mixture was shaken at room temperature (31°) for 5.5 hr. at an initial pressure of 60 p.s.i. The catalyst was filtered, rinsed with water (2–20 ml.), and the filtrates were combined. After cooling in an ice bath, the filtrate was acidified (pH 6) with 10% hydrochloric acid. The unchanged phloroglucinol was filtered, and water was added to make the total volume of the solution 350 ml. Attempts to obtain the diketone by neutralization of the salt resulted only in polymeric material, so it was necessary to isolate the sodium salt.

Into ten 250-ml. round-bottom flasks was placed 35 ml. of this solution and the water was removed by freeze drying (0.03 mm.) for 18 hr. Fifty milliliters of a solution of 40% ethyl acetate–60% ethyl alcohol was added to each flask, stirred for 30 min., filtered, and the maroon residue was rinsed with a small amount of ethyl acetate–ethyl alcohol mixture. This dark red filtrate was poured with stirring into ethyl acetate (about 1 l.); the sodium salt of dihydrophloroglucinol (V) was filtered rapidly and dried under reduced pressure (0.02 mm.).

Based on the recovered phloroglucinol, the yield of monosodiodihydrophloroglucinol (V) was 98%. This salt is quite hygroscopic and necessitates storage *in vacuo*, $\lambda_{max.}^{EtOH}$ 280 mμ (ε 18,800).

2-Benzyl-5-hydroxycyclohexane-1,3-dione (VI).—The procedure (9) for the preparation of 2-benzylcyclohexane-1,3-dione (X) was modified as follows. In a 100-ml. round-bottom flask fitted with a condenser and magnetic stirrer was placed 7.7 Gm. (0.057 mole) of monosodiodihydrophloroglucinol, 7.0 ml. (0.06 mole) of benzyl chloride, 8.0 ml. of water, and 0.4 Gm. (0.24 mmole) of potassium iodide. The mixture was stirred for 2 hr. in an oil bath (95°), cooled to room temperature, and 5% sodium hydroxide was added until the mixture was distinctly alkaline (pH 9–10). The gummy mixture was extracted with two 50-ml. portions of ether and the ether solutions were discarded. The dark alkaline solution was cooled to 5° in an ice bath and made acidic (pH 2) with 10% hydrochloric acid. A viscous brown oil separated after the flask stood in the refrigerator for several hours. The aqueous solution was decanted and 25 ml. of chloroform was added to the oil. After standing at room temperature for 12 hr., yellow crystals separated. The crystals were dissolved in a small amount of ethyl acetate, heated to boiling, petroleum ether was added to the cloud point, the mixture was allowed to cool to room temperature, and then placed in a

refrigerator for 2–3 hr. The yellow crystals were recrystallized from ethyl acetate–petroleum ether in the same manner, affording 2.0 Gm. (18%) of the alkylated dione (VI), m.p. 161°; $\lambda_{max.}^{EtOH}$ 263 mμ (ε 12,800), $\lambda_{max.}^{EtOH}$ 289 mμ (ε 23,200). The infrared spectrum (Nujol mull) of this material exhibited a broad band at 3.2 μ (bonded OH) and a sharp band at 14.2 μ (mono-substituted benzene).

Anal.—Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.79; H, 6.91.

Attempted Preparation of 3-Hydroxy-5-oxo-7-phenylheptanoic Acid (VII).—The procedure (9) for the preparation of 5-oxo-7-phenylheptanoic acid (XI) was followed using 0.486 Gm. (2.23 mmoles) of 2-benzyl-5-hydroxycyclohexane-1,3-dione (VI), 3.2 Gm. (10.7 mmoles) of barium hydroxide octahydrate, and 10 ml. of freshly distilled water. After stirring for 25 hr. at 105–110° the mixture was cooled in an ice bath and 10% hydrochloric acid was added dropwise to a Congo red end point. The cloudy aqueous solution was extracted with three 25-ml. portions of ether, the combined ether solutions dried over anhydrous magnesium sulfate, and the ether was evaporated. A dark viscous oil (350 mg.) was obtained which had a sweet odor but which would not form a 2,4-DNP derivative.

This oil did not solidify and crystallization could not be induced. It was insoluble in 20% sodium bicarbonate, but was soluble in 5% sodium hydroxide. The infrared spectrum (liquid film) exhibited absorption at 3.0 (OH), 5.9 (C=O), and 14.3 μ (monosubstituted benzene). It was not possible to purify this material.

2-(p-Nitrobenzyl)-5-hydroxycyclohexane-1,3-dione (XIII).—A solution of 4.5 Gm. (0.026 mole) of *p*-nitrobenzyl chloride dissolved in 20 ml. of DMF was added to a stirred solution of 3.5 Gm. (0.026 mole) of monosodiodihydrophloroglucinol in 30 ml. of DMF. After stirring 24 hr. at room temperature (25°) the sodium chloride was filtered and the DMF was removed under reduced pressure. Chloroform was added to the residue, heated to boiling, and decanted from the dark insoluble material. This was repeated twice, and the chloroform extracts were combined. The yellow organic solution was heated to boiling, petroleum ether was added to the cloud point, and the mixture was allowed to cool to room temperature; it was then placed in a refrigerator. The crystals were filtered and the filtrate was treated in the same manner twice again. The three crops of crystals were combined and recrystallized twice from ethyl acetate, affording 2 Gm. (30%) of the dione (XIII), m.p. 184–185°; $\lambda_{max.}^{EtOH}$ 265 mμ (ε 37,400), $\lambda_{max.}^{alk.\ EtOH}$ 287 mμ (ε 64,800). The crystalline material gave a negative Beilstein (halogen) test and exhibited strong bands in the infrared spectrum (Nujol mull) at 6.45 and 7.4 μ (aromatic nitro).

Anal.—Calcd. for $C_{13}H_{13}NO_5$: C, 59.32; H, 4.98; N, 5.32. Found: C, 59.80; H, 5.06; N, 5.28.

Attempts to prepare the keto-acid (XIV) from the dione (XIII) by means of a reverse Claisen reaction using barium hydroxide as the base were unsuccessful.[1]

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[1] Melting points were obtained on a calibrated Thomas-Hoover Unimelt and are corrected. Infrared data were recorded on Beckman IR5 and IR8 spectrophotometers. Ultraviolet data were recorded on a Bausch & Lomb 505 spectrophotometer. Microanalyses were conducted by Drs. G. Weiler and F. B. Strauss, Oxford, England.