(45%) of a viscous oil. This material traveled as a single spot on Whatman No. 1 paper, R_f 0.80 in *n*-butanol saturated with water. In a larger scale preparation, VII crystallized, m.p. 122–124°.

A crystalline picrate of this oil was prepared by adding a saturated solution of picric acid in ethanol to a 10% solution of the oil in ethanol, m.p. 187.5–188.5°; $\lambda_{max(\mu)}^{Nujol}$ 2.82 (OH), 3.48 (NH^+), 6.18 (aryl), 6.51 (NO_2), 9.40 (C—OH).

Anal. Calcd. for $C_{10}H_{12}N_2OS \cdot C_6H_3N_3O_7$: C, 43.9; H, 3.45; N, 16.0; S, 7.33. Found: C, 44.1; H, 3.71; N, 16.1; S, 7.11.

2-[(2-Chloroethyl)thiomethyl]benzimidazole hydrochloride (VIII). To a solution of 4.66 g. (0.023 mol.) of VII in 60 ml. of chloroform was added dropwise with stirring a solution of 22.8 ml. (0.32 mol.) of thionyl chloride in 35 ml. of chloroform. After the addition was complete, the reaction mixture was refluxed for 4 hr., then allowed to stand overnight at room temperature. The system was filtered to yield 4.76 g. (81%) of product, m.p. 177–179°.

An analytical sample was prepared by recrystallization of the crude product from methanol saturated with hydrogen chloride at 40° by the addition of hot benzene, m.p. 180–182°; $\lambda_{max(\mu)}^{Nujol}$ 6.10, 6.35 (aryl, C=N), 13.35 (*o*-disubstituted benzene), no C—OH near 9.40 nor OH near 2.8.

Anal. Calcd. for $C_{10}H_{11}ClN_2S \cdot HCl$: C, 45.6; H, 4.59; Cl, 26.9, S, 12.2. Found: C, 45.7; H, 4.70; Cl, 27.3; S, 11.7.

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Piper Methysticum Forst. II. The Synthesis of *dl*-Methysticin and *dl*-Dihydromethysticin

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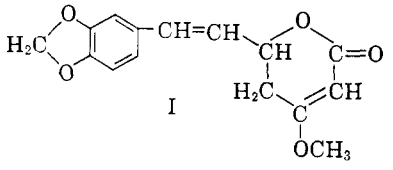
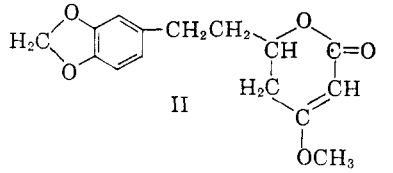
In a previous paper from these laboratories[1] the results of a chemical and pharmacological investigation of *Piper methysticum* Forst were reported. On the basis of ability to antagonize strychnine convulsions and potentiate barbiturate sleep time in mice, it was found that methysticin I and



I



II

dihydromethysticin II possessed a greater degree of activity than the other constituents, kawain, dihydrokawain, yangonin, and desmethoxyyangonin,[2] isolated from this plant. The significant physiological activity evidenced by methysticin and dihydromethysticin on the central nervous system made it of interest to obtain sufficient quantities of these α-pyrone derivatives for further pharmacological studies. Because of the inherent difficulties attendant in securing these compounds from their natural source, a means for obtaining them synthetically was desirable.

The synthesis of kawain[3] and yangonin[4] have been recorded by previous investigators, but the synthesis of methysticin, the first of this class of compounds to be isolated from this plant[5] and its dihydro derivative have not been reported, although their structures have been known since 1929.[6]

Our approach to the synthesis of *dl*-methysticin was by the Reformatsky condensation of 3,4-methylenedioxycinnamaldehyde and methyl γ-bromo-β-methoxycrotonate using tetrahydrofuran as the reaction medium. The condensation proceeded smoothly and *dl*-methysticin was readily obtained by direct crystallization of the product. A comparison of the infrared and ultraviolet spectra of this compound with those of natural methysticin showed them to be indistinguishable. Further evidence for confirming their structural identity was obtained by removing the center of asymmetry at C_6 in the α-pyrone ring of methysticin, by basic hydrolysis, thereby forming methysticic acid which proved to be identical with the acid obtained in the same manner from *dl*-methysticin.

Catalytic reduction of *dl*-methysticin afforded *dl*-dihydromethysticin which exhibited the same infrared and ultraviolet spectra as those of the naturally occurring material.

EXPERIMENTAL[7]

6-(3',4'-Methylenedioxystyryl)-4-methoxy-5,6-dihydro-2-H-pyran-2-one. 3,4-Methylenedioxycinnamaldehyde (58.6 g.;

(1) M. W. Klohs, F. Keller, R. E. Williams, I. M. Toekes and G. E. Cronheim, *Journal of Medicinal and Pharmaceutical Chemistry*, 1, 95 (1959).

(2) This substance had been referred to as compound A in our earlier paper, pending final identification. Compound A has now been compared with a synthetic sample of desmethoxyyangonin [J. Cieślak, *Roczniki Chemii*, 32, 837 (1958) and references therein kindly supplied by Dr. Jerzy Cieślak and they have been found to be identical. This represents the first recorded occurrence of desmethoxyyangonin in *P. methysticum*. Since the completion of this work a publication has appeared citing the presence of this compound in *Aniba firmula* Mez. [Otto Richard Gottlieb and Walter B Mors, *J. Org. Chem.*, 24, 17–18 (1959)].

(3) D. Kosterman, *Nature*, 166, 787 (1950); D. Kosterman, *Rec. Trav. Chim.* 70, 79 (1951); E. M. P. Fowler and H. B. Henbest, *J. Chem. Soc.*, 3642 (1950).

(4) W. Borsche and C. K. Bodenstein, *Ber.* 62, 2515 (1929).

(5) Gobley and O'Rorke, *J. de Pharmacie et Chimi*, 598 (1860), M. Cuzent, *Compt. rend.* 205 (1861).

(6) W. Borsche and W. Peitzsch, *Ber.*, 62, 360 (1929).

(7) All microanalyses by H. V. Tashinian, Microchemical Specialties Company, Berkeley 3, California.

0.33 mole) and methyl-γ-bromo-β-methoxortcyonate,[8] (70 g.; 0.33 mole) were dissolved in 1 liter of tetrahydrofuran (tetrahydrofuran was distilled from calcium hydride and mineral oil and stored over sodium prior to use). This solution was added dropwise through a dropping funnel into a dry 3-neck round bottom flask, equipped with stirrer and reflux condenser and containing finely cut zinc sheet metal (25 g.; 0.38 mole); the zinc metal, immediately prior to the reaction, was sanded, cut into small strips and washed consecutively with 25% hydrochloric acid, water, methanol, acetone and ether, and then dried at 100°. A small crystal of iodine was added to help initiate the reaction and the solution was refluxed with stirring for 5 hr. At the end of this time the reaction mixture (reddish-brown in color) was cooled to room temperature and added to a saturated solution of ammonium chloride (2.5 l.) with stirring. The mixture was extracted twice with $CHCl_3$ (1500 ml. portions) and the combined $CHCl_3$ extracts were washed once with water (500 ml.), filtered through anhydrous sodium sulfate and concentrated on the steam bath *in vacuo* to a resinous mass which on standing overnight at room temperature formed a solid mass of crystals. The material was triturated with ether (500 ml.), filtered and recrystallized from methanol (350 ml.) to give 35 g. (38%) of *dl*-methysticin, m.p. 132–134°. The ultraviolet spectrum showed $\lambda_{max.}^{alc.}$ (log ε): 226 mμ (4.40), 267 mμ (4.14), 306 mμ (3.93); $\lambda_{min.}^{alc.}$ (log ε): 218 mμ (4.37), 253 mμ (4.09), 284 mμ (3.80).

Anal. Calcd. for $C_{15}H_{14}O_5$: C, 65.59; H, 5.15; —OCH_3, 11.23; M.W., 274. Found: C, 65.56; H, 5.25; —OCH_3, 11.35; M.W. (Rast), 285.

A comparison of the ultraviolet and infrared absorption spectra of this material with those of an authentic sample of natural methysticin showed them to be identical.

7-(3',4'-methylenedioxyphenyl)-3-methoxy-2,4,6-heptatrienoic acid-1. *dl*-Methysticin was hydrolyzed by the procedure employed by Borsche and co-workers for the hydrolysis of natural methysticin,[9] giving a nearly quantitative yield of methysticic acid. The light yellow crystalline product was recrystallized from hot methanol; m.p. 196–197°.

Anal. Calcd. for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15. Found: C, 65.54; H, 5.31.

Upon admixture with an authentic sample of methysticic acid, no depression of melting point was observed. The infrared and ultraviolet absorption spectra were identical.

6-(3',4'-Methylenedioxy-β-phenethyl)-4-methoxy-5,6-dihydro-2-H-pyran-2-one. dl-Methysticin (300 g.) was dissolved in tetrahydrofuran (1.2 l.) and 10% Pd on carbon catalyst (10 g.) was added. The mixture was hydrogenated on a modified Parr apparatus at a pressure of 35 p.s.i., the uptake being completed within one hour. The solution was filtered free of suspended catalyst and the filtrate was taken to dryness *in vacuo* yielding crystals. The crude product was recrystallized from isopropyl alcohol (1.5 l.) to give needles (270 g.), m.p. 110–111°.

Anal. Calcd. for: $C_{15}H_{16}O_5$: C, 65.21; H, 5.84; —OCH_3, 11.23. Found: C, 64.99; H, 5.85; —OCH_3, 11.74.

The infrared and ultraviolet absorption spectra of this material were identical with those of an authentic sample of natural dihydromethysticin.

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(8) F. Kogl and O. A. de Bruin, *Rec. Trav. Chim.* **69**, 729 (1950) *Chem. Abs.* **45**, 2416 (1951).

(9) W. Borsche, C. H. Meyer, and W. Peitzsch, *Ber.*, **60**, 2113 (1927).

Novel Rearrangement in the Oxidation of 3-Butylideneacetylacetone by Hydrogen Peroxide

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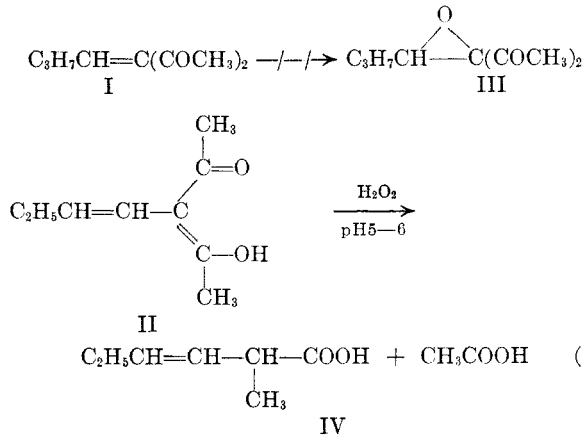
As part of a general survey concerned with the mode of reaction of various unsaturated materials with hydrogen peroxide under controlled *p*H conditions, the product from the condensation of *n*-butyraldehyde with acetylacetone was investigated. It was initially assumed that this product, 3-butylideneacetylacetone, would have structure I, and that it would probably afford the corresponding epoxy diketone (III) on treatment with hydrogen peroxide at the appropriate *p*H.



Surprisingly, *2-methyl-3-hexenoic acid* (IV) rather than III was obtained in 70% yield by the action of hydrogen peroxide at *p*H 5–6 and 38–40° for 1 hr. In view of this result, perhaps the structure of the starting material was not correctly described.

That II, 3-acetyl-2,4-heptadien-2-ol, should better represent this structure was indicated by analogy with the products obtained earlier from the reactions of propionaldehyde[1] and isovaleraldehyde[2] with acetylacetone. This belief was confirmed by infrared analysis which showed the condensation product to possess a highly enolized β-diketone system.[3]

Structure IV was established on the basis of physical constants and analysis as well as by direct comparison of its anilide and saturated anilide with authentic samples.

Confirmation of the position of the double bond in IV was obtained by treatment with iodine-sodium bicarbonate[4] to give the iodo lactone (V) in 87%

(1) M. E. McEntee and A. R. Pinder, *J. Chem. Soc.*, 4419 (1957).

(2) F. Tiemann and P. Krüger, *Ber.*, **28**, 2121 (1895).

(3) L. J. Bellamy, "Infrared Spectra of Complex Molecules," J. Wiley and Sons, Inc., New York, 1954, p. 123.

(4) R. P. Linstead and C. J. May, *J. Chem. Soc.*, 2565 (1927).