Synthesis of Some α,β-Unsaturated β,δ-Disubstituted δ-Lactones

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A series of 18 new α,β-unsaturated β,δ-disubstituted δ-lactones was synthesized as possible therapeutic agents. The majority of the compounds described contain an aryloxy group in the β-position of the lactone ring, while those naturally occurring in *Piper methysticum* all contain an alkoxy group in this position. Some of the lactones were hydrogenated by means of palladium-on-charcoal to the corresponding dihydro derivatives. The infrared absorption spectra of most of the synthesized compounds were also studied.

PIPER METHYSTICUM Forst. of the family *Peiperaceae* is a shrub common to the islands of Indonesia where it is known in various dialects as kawa, kava, or ava. The rest of the kawa plant has been held in high esteem by the Polynesians from ancient times for its use in preparing an extract, which upon drinking, is reported to reduce fatigue and produce complete freedom from anxiety (1).

"The National Standard Dispensatory" of 1909 (2) describes *P. methysticum* and lists as a pharmaceutical preparation fluid extract of kava N.F. The same edition has a long list on action and uses of the drug.

Marpmann demonstrated in 1905 (3) that the constituent kawain possesses bacteriological properties, especially for the gonococcus, but also for the *Coli bacillus*.

The remarkable physiological action of *P. methysticum* has prompted numerous chemical investigations, dating from an article by Gobley in 1860 (4). The most extensive work on the constituents of this plant was carried out by W. Borsche and his co-workers, who in a series of 14 papers extending over a period of 19 years (1914–1933) reported the isolation and structure of two new compounds, kawain (Gonosan) and dihydrokawain (DHK). These workers also elucidated the structures of other crystalline components, methysticin, dihydromethysticin (DHM), and yangonin, which had previously been isolated from this plant. At the conclusion of his work, Borsche stated that all of these compounds failed to exhibit the typical physiological action of the kawa root (5). In a later study, using chromatographic techniques, Van Veen isolated a substance "marindinin"[1] which when administered in a lecithin-water emulsion in the amount of 50–70 mg. to pigeons and in the amount of 500 mg. to monkeys (weighing 1 Kg.), exhibited the characteristic action of kawa (6). This compound was shown to be identical with dihydrokawain previously isolated by Borsche. Hansel and Beiersdorff (7) showed that dihydromethysticin is another active ingredient of the root. Besides the compounds already mentioned, Klohs and co-workers (8) succeeded in isolating a small quantity of a new compound which was designated as "compound A" and later shown to be desmethoxyyangonin (9).

As can be seen from Fig. 1 all the naturally occurring lactones of known structure are α-pyrones except for yangonin and desmethoxyyangonin which belong to the γ-pyrone series.

The structural determination of the kawa lactones was exclusively determined by degradation of the molecule and the final proof for kawain was accomplished by synthesis in 1950 and for methysticin and dihydromethysticin in 1959 (10, 11). Another synthesis of kawain by a different method was announced in 1951 (12).

EXPERIMENTAL[2]

Ethyl β-Chlorocrotonate.—This compound was prepared by a modification of the method used by Thomas-Mamert (13) resulting in an improved yield. In a dry 1-L. round-bottom, three-necked flask equipped with a reflux condenser and placed under the hood 200 Gm. (0.154 mole) of ethyl acetoacetate and 400 ml. of petroleum ether (b.p. 30–60°) were added. To this mixture 170 Gm. (0.816 mole) of phosphorus pentachloride was gradually added. Upon completion of the reaction, 500

Received June 3, 1963, from the School of Pharmacy, University of North Carolina, Chapel Hill.
Accepted for publication October 16, 1963.
This project was initiated under the direction of the late Dr. Sigurdur Jonsson, School of Pharmacy, University of North Carolina, Chapel Hill.
Abstracted in part from a thesis submitted by Vilhjalmur G. Skulason to the Graduate School, University of North Carolina, in partial fulfillment of Master of Science degree requirements.
This investigation was supported in part by the following organizations: the National Science Foundation, the University of North Carolina Research Council, the Harald Quintus Besz Memorial Foundation, Utrecht, Holland, and the North Carolina Pharmaceutical Research Foundation.
Presented to the Scientific Section, A. PH. A., Miami Beach meeting, May 1963.

[1] Named after the Marindines tribe of Netherlands New Guinea.

[2] All melting points were taken with the Mel-Temp apparatus and are uncorrected as are the boiling points. The microanalyses were performed by Drs. Weiler and Strauss, Microanalytical Laboratories, Oxford, England. The infrared spectra were determined on a Perkin-Elmer model 137B spectrophotometer using 2.5% solution in chloroform and sodium chloride cell.

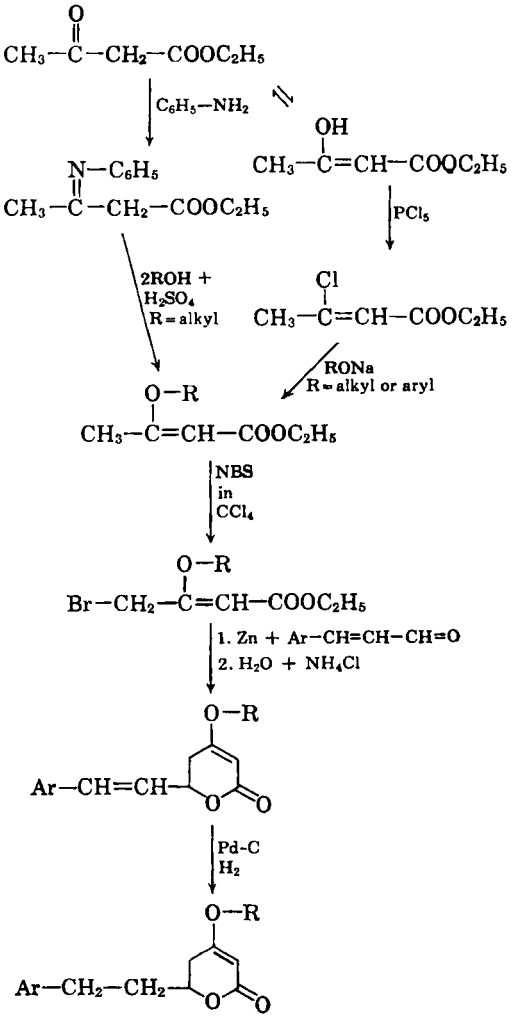
ml. of water was added in small portions, transferred to a separator, and the layers separated, followed by washing the aqueous layer with three 100-ml. portions of petroleum ether (b.p. 30–60°). The combined yellow petroleum ether extracts were washed with a 20% potassium carbonate solution, dried over anhydrous sodium sulfate, then evaporated *in vacuo*. Distillation of the residue gave 48% of a colorless liquid with a pungent odor, which on standing turns green, b.p. 163–176°.

Anil of Ethyl Acetoacetate.—This compound was prepared by a method previously described in the literature and used without further purification for the preparation of ethyl β-methoxycrotonate and ethyl β-ethoxycrotonate (14).

Ethyl β-n-Propoxycrotonate and Ethyl β-Isopropoxycrotonate.—These compounds were prepared essentially by the method of Koll (15).

A general method was employed in the preparation of all compounds listed in Tables I and II. The method used is illustrated below for the synthesis of ethyl β-*p*-chlorophenoxycrotonate and ethyl-γ-bromo β-*p*-chlorophenoxycrotonate, respectively.

Ethyl β-p-Chlorophenoxycrotonate.—This compound was prepared by a modification of a method



Reaction Sequence Used in Present Synthesis

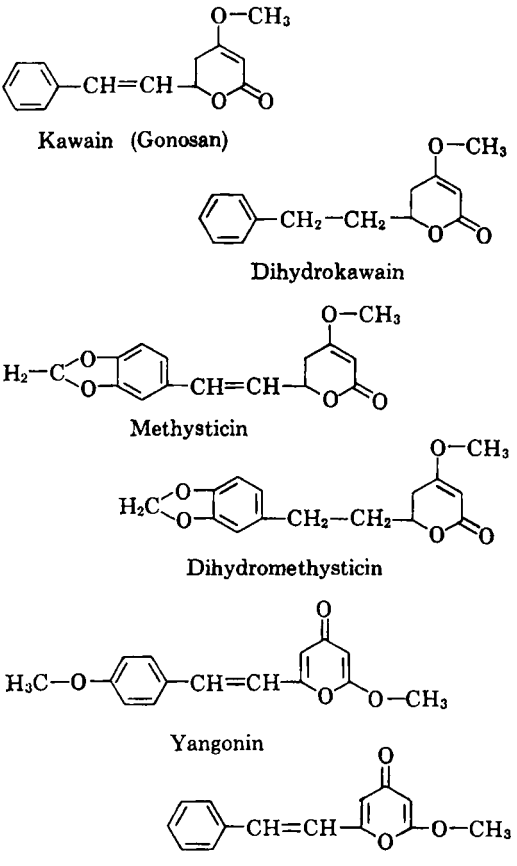
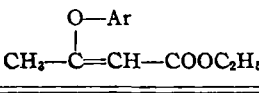


Fig. 1.

described in the literature (14). To 11.5 Gm. (0.5 Gm. At.) of sodium dissolved in 200 ml. of ethanol, 65 Gm. (0.505 mole) of *p*-chlorophenol, and 85 Gm. (0.572 mole) of ethyl β-chlorocrotonate were added. This mixture was heated on the steam bath for 2 hours, at which time the mixture was almost neutral to litmus. The sodium chloride was filtered, the alcohol removed by distillation, and the resulting product triturated with water and extracted with ether. Unreacted phenol was removed from the ether layer by shaking it twice with 100-ml. portions of 5% solution of sodium hydroxide. The ether solution was dried over anhydrous sodium sulfate and evaporated. Distillation of the residue gave 53% of a colorless oil, b.p. 110–117° (0.8 mm.)

Ethyl γ-Bromo β-p-Chlorophenoxycrotonate.—This compound was prepared by a modification of the procedure described by Kogl and deBruin (16). In a dry 1-L. round-bottom flask fitted with a reflux condenser, 200 ml. of carbon tetrachloride and 98 Gm. (0.407 mole) of ethyl β-*p*-chlorophenoxycrotonate were added. To this solution 73 Gm. (0.410 mole) of *N*-bromo-succinimide and 8 Gm. (0.033 mole) of benzoyl peroxide were added and the mixture heated on the water bath for 3 hours. The reaction mixture was then placed in the refrigerator overnight, the succinimide removed by filtration, and the solvent distilled *in vacuo*. Distillation of the residue gave 71% of a faint greenish liquid, b.p. 140–160° (0.15 to 0.25 mm.). After several

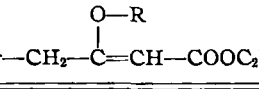
TABLE I.—ETHYL β-ARYLOXYCROTONATES



Ar	Formula	B. p.	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	Yield, %
p-Cl—C_6H_4—	$C_{12}H_{13}ClO_3$	110–117 (0.8 mm.)	59.88	59.80	5.44	5.41	53[a]
o-CH_3—OC_6H_4—	$C_{13}H_{16}O_4$	120–132 (0.8 mm.)	66.09	66.00	6.82	6.79	55
p-CH_3—C_6H_4—	$C_{13}H_{16}O_3$	70– 98 (0.1 mm.)	70.88	70.73	7.32	7.26	51
p-*n*-C_4H_9—O—C_6H_4—	$C_{16}H_{22}O_4$	139–147 (0.05 mm.)	69.04	68.94	7.97	7.90	47

[a] Calcd. for Cl: 14.73. Found: 14.68.

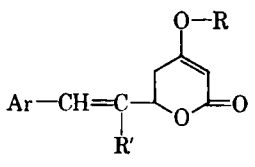
TABLE II.—ETHYL γ-BROMO β-ALKOXY (OR ARYLOXY) CROTONATES



R	Formula	B. p.	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	Br, % Calcd.	Br, % Found	Yield, %
CH_3—	$C_7H_{11}BrO_3$	68– 72 (0.1 mm.)	37.69	37.65	4.97	4.93	35.82	35.78	78[a]
C_2H_5—	$C_8H_{13}BrO_3$	79– 84 (0.15–0.05 mm.)	40.52	40.49	5.53	5.47	33.70	33.66	75[a]
n-C_3H_7—	$C_9H_{15}BrO_3$	165–170 (33 mm.)	43.04	42.95	6.02	5.98	31.82	31.73	[c]
i-C_3H_7	$C_9H_{15}BrO_3$	150–154 (35 mm.)	43.04	42.99	6.02	5.95	31.82	31.69	[c]
C_6H_5	$C_{12}H_{13}BrO_3$	108–124 (0.3 mm.)	50.55	50.51	4.59	4.56	28.02	28.00	[c]
p-CH_3—C_6H_4—	$C_{13}H_{15}BrO_3$	127–140 (0.3 mm.)	52.19	52.08	5.05	5.00	26.71	26.68	39
o-CH_3—O—C_6H_4—	$C_{13}H_{15}BrO_4$	123–154 (0.35 mm.)	49.54	49.50	4.80	4.78	25.36	25.27	58
p-Cl—C_6H_4—	$C_{12}H_{12}BrClO_3$	140–160 (0.15–0.25 mm.)	45.10	45.08	3.78	3.75	25.00	24.93	71[a,b]
p-*n*-C_4H_9—O—C_6H_4—	$C_{16}H_{21}BrO_4$	190–193 (0.40–0.55 mm.)	53.79	53.73	5.92	5.89	22.37	22.29	42

[a] Benzoyl peroxide was used as a catalyst. [b] Calcd. for Cl: 11.09. Found: 11.00. [c] Yields not calculated.

TABLE III.—α,β-UNSATURATED β,δ-DISUBSTITUTED δ-LACTONES



Ar	R′	R	M.p., °C.	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	C, % Calcd.	C, % Found	Yield, %
C_6H_5—	H	CH_3—	145–146[a,b]	...	...	...	...	...	...	17
C_6H_5—	H	C_2H_5—	99–100	73.77	74.03	6.56	6.37	...	...	5
C_6H_5—	H	*n*-C_3H_7—	77– 78	74.42	74.25 74.29	7.05	7.13 7.16	...	...	6
C_6H_5—	H	*i*-C_3H_7—	94– 95	74.42	74.14	7.05	7.25	...	...	5
C_6H_5—	H	C_6H_5—	135–136	78.08	77.83 77.44	5.48	5.58 5.50	...	...	12
C_6H_5—	H	*p*-CH_3—C_6H_4—	128–129	78.43	78.45	5.88	5.75	...	...	20
C_6H_5—	H	*o*-CH_3—O—C_6H_4—	144–145	74.54	74.26 74.32	5.65	5.71 5.86	...	...	13
C_6H_5—	H	*p*-Cl—C_6H_4—	150–151	69.81	69.71 69.75	4.64	4.59 4.73	10.86	11.05 11.20	17
C_6H_5—	CH_3—	C_2H_5—	74– 76	74.39	74.28 74.41	7.02	7.32 7.40	...	...	8
	H	C_2H_5—	86– 87	66.65	67.16 67.04	6.02	5.84 5.89	...	...	2
C_6H_5—	CH_3—	*p*-Cl—C_6H_4—	167–168	70.44	69.66 69.86	5.03	4.69 4.85	10.40	11.22 11.25	45
	H	*p*-Cl—C_6H_4—	122–124	64.46	64.13 64.31	4.14	4.11 4.26	11.19	11.11 11.15	8
C_6H_5—	CH_3—	CH_3—	133–135	73.75	73.51 73.67	6.60	6.57 6.66	...	...	17
C_6H_5—	Br—	*p*-Cl—C_6H_4—	173–174	56.25	56.51 56.70	3.48	3.76 3.88	...	...	27
C_6H_5—	CH_3—	*p*-*n*-C_4H_9—O—C_6H_4—	107–108[c]	76.16	76.13 76.48	6.93	6.93 6.95	...	...	10

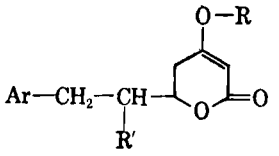
[a] Melting point reported in the literature is 146–147° (6). [b] All the compounds listed in Table III gave a strong characteristic red when a few crystals were dropped on concentrated sulfuric acid in a test tube. [c] The synthesis of this compound required the addition of magnesium and iodine to initiate the reaction.

days at room temperature the compound turned to a solid, m.p. 30°.

4 - p - Chlorophenoxy - 6 - β - methylstyryl-5,6-dihydro-2-pyrone.—To a completely dry 500-ml. round-bottom flask fitted with a reflux condenser and a calcium chloride drying tube, 6.5 Gm. of completely dry and activated zinc metal granules (40-mesh) was added.[3] To this was added a solution of 32 Gm. (0.100 mole) of ethyl γ-bromo-β-*p*-chlorophenoxy-crotonate and 15 Gm. (0.102 mole) of

[3] The activated zinc was obtained by allowing 10% hydrochloric acid to act on it for 10 minutes, washing it thoroughly with water, acetone, alcohol, and anhydrous ether, respectively. Finally, it was dried in a vacuum oven at 100°.

TABLE IV.—α,β-UNSATURATED β,δ-DISUBSTITUTED δ-LACTONES



Ar	R′	R	M.p., °C.	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	C, % Calcd.	C, % Found	Yield, %
C_6H_5—	H	CH_3—	74–75[a]	72.39	72.56 72.74	6.86	7.26 7.35	...	...	82
C_6H_5—	H	*p*-CH_3—C_6H_4—	120–122	77.89	77.66 77.75	6.55	6.73 6.84	...	...	92
C_6H_5—	CH_3—	*p*-Cl—C_6H_4—	135–137	70.07	69.79 69.93	5.59	5.66 5.88	10.34	10.48 10.61	74
C_6H_5—	H	*p*-Cl—C_6H_4—	119–120	69.41	69.46 69.53	5.21	5.31 5.62	10.78	10.48 10.50	100
C_6H_5—	H	*o*-CH_3—O—C_6H_4—	103–105	74.06	73.85 73.95	6.21	6.67 6.82	...	...	69

[a] Melting point reported in the literature is 76° (3).

freshly distilled α-methylcinnamaldehyde in 200 ml. of tetrahydrofuran which had been previously distilled over mineral oil. This mixture was heated to its boiling point, whereupon a small crystal of iodine was introduced to help initiate the reaction. It was then refluxed with occasional shaking for 5 hours. At the end of the reflux time, 5.9 Gm. of the zinc had dissolved. The mixture was cooled to room temperature and added with stirring to 600 ml. of a saturated solution of ammonium chloride. After extracting three times with chloroform (200 ml. and 2 times 100 ml.), the combined chloroform extracts were washed once with 200 ml. of water, dried over and filtered through anhydrous sodium sulfate, and concentrated *in vacuo* to a small volume. The residue was placed in the refrigerator overnight causing crystals to separate. After washing with methanol and drying, the crystals had m.p. 164–166°. A second crop of crystals was obtained by evaporating the methanol solution and placing it in the refrigerator. Further recrystallization from a mixture of chloroform-ether afforded 45% of white crystals, m.p. 167–168°. The compounds listed in Table III were prepared in an analogous manner.

4-p-Tolyloxy-6-phenethyl-5,6-dihydro-2-pyrone.—A solution of 4.3 Gm. (0.013 moles) of 4-*p*-tolyloxy-6-styryl-5,6-dihydro-2-pyrone in 30 ml. of tetrahydrofuran was treated with 0.2 Gm. of 15% palladium-carbon catalyst and hydrogenated at 30 p.s.i. After 2.5 hours, the mixture had taken up one molecular equivalent of hydrogen. The catalyst was removed by filtration, and the solvent was distilled *in vacuo*. Recrystallization of the residue from tetrahydrofuran gave 92% of product, m.p. 48–49°. Table IV lists the compounds prepared by the above method.

Infrared Absorption Spectra.—The infrared absorption spectra of all the lactones with a saturated side chain are similar to those with an unsaturated side chain, except for the absence of the absorption band at 10.38 μ, which is assigned to the *trans* configuration of the unsaturated lactones, and consequently is absent in the saturated ones. The strong absorption bands at 5.90 and 6.17 μ are common to all the lactones and are assigned to the C=O group in conjugation with the C=C grouping, respectively.

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