[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

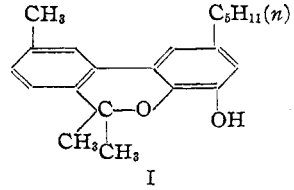
Structure of Cannabidiol, a Product Isolated from the Marihuana Extract of Minnesota Wild Hemp. I

BY ROGER ADAMS, MADISON HUNT, AND J. H. CLARK[1]

(IN COLLABORATION WITH THE TREASURY DEPARTMENT, NARCOTICS LABORATORY, WASHINGTON, D. C., AND DR. S. LOEWE, DEPT. OF PHARMACOLOGY, CORNELL UNIVERSITY MEDICAL COLLEGE)

Marihuana is the term commonly used in the United States to represent those portions of the *Cannabis sativa* or hemp plant which are capable of inducing somatic and psychic changes in humans. It is also familiarly known as hashish, bhang, charas, and ganja. The activity of an extract of the plant is found to vary widely, and to be dependent on the source of the hemp. Previous investigators, for the most part, have studied the resin obtained by working up hashish of Indian origin from the variety of hemp known as *Cannabis indica*. In this investigation, Minnesota wild hemp, cut after flowering had begun and before the seed had "set" in the female tops, was used as a raw material. It was extracted with ethanol and the so-called "red oil" containing the active principle or principles was obtained by distillation under diminished pressure.

Numerous investigators have studied the active red oil from *Cannabis sativa* and *indica* but only a single pure substance other than nonacosane has yet been isolated from the mixture of products present. This was called cannabinol by Wood, Spivey and Easterfield,[2] and was purified through its crystalline acetate. They assigned the formula $C_{21}H_{26}O_2$. This formula was confirmed and the constitution investigated by Cahn,[3] who proposed structure I in which the positions of the hydroxyl and *n*-amyl groups are uncertain.



I

Cannabinol is very toxic but has no marihuana activity. A knowledge of the structure of this compound is significant, however, due to the fact that the active red oil, even though derived from various sources, gives an analysis not substantially different from that of pure cannabinol.

When the red oil from Minnesota hemp was treated to isolate cannabinol according to methods previously suggested, no crystalline cannabinol acetate[3] or *p*-nitrobenzoate[4] could be isolated. Since the red oil contained substances with phenolic groups as shown by qualitative tests, other reagents for phenols were studied. This resulted in observing that a crystalline 3,5-dinitrobenzoyl derivative could be isolated in yields which corresponded to about 33% of the purified red oil used. Analysis indicated this derivative to be a *bis*-3,5-dinitrobenzoate of a dihydric phenol of the formula $C_{21}H_{30}O_2$ or $C_{21}H_{32}O_2$, the analysis not allowing distinction between them. It was readily purified. Upon ammonolysis of the purified *bis*-3,5-dinitrobenzoate by means of ammonia in toluene, the isolation of a pure compound was accomplished. It proved to have one of the two empirical formulas suggested above and has been given the name cannabidiol. It has none of the physiological activity typical of marihuana. The product is optically active, $[\alpha]_D$ $-119°$, and gives a very strong alkaline Beam test somewhat different from and more intense than that exhibited by purified red oil. Numerous other color tests applied to cannabidiol and purified red oil are given in Table I. It is obvious that the colors given by the red oil are dependent in part on substances other than cannabidiol.

By comparison with the formula of cannabinol, it is obvious that cannabidiol contains merely four or six more hydrogen atoms. The presence of two hydroxyls, presumably phenolic, is shown by the *bis*-3,5-dinitrobenzoate derivative and further was confirmed by the preparation of a crystalline *bis*-*m*-nitrobenzene sulfonate, a dimethyl ether, and a Zerewitinoff determination.

Methylation by means of repeated treatments with excess methyl iodide in acetone and potas-

(1) An abstract of a thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry. Solvay Process Company Fellow, 1939–1940.

(2) Wood, Spivey and Easterfield, *J. Chem. Soc.*, **69**, 539 (1896); **75**, 20 (1899).

(3) Cahn, *ibid.*, 986 (1930); 630 (1931); 1342 (1932); 1400 (1933). See also Bergel, *Ann.*, **482**, 55 (1930); **493**, 250 (1932). An excellent review of the literature dealing with the chemical constituents of *Cannabis sativa* is given in an article by Blatt, *J. Wash. Acad. Sci.*, **28**, 465 (1938).

(4) Work, Bergel and Todd, *Biochem. J.*, **33**, 123 (1939).

TABLE I

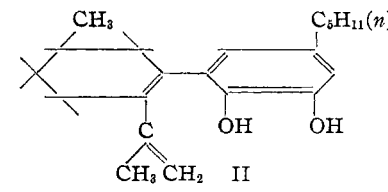
COLOR REACTIONS OF CANNABIDIOL AND OF PURIFIED RED OIL

Test	Red oil	Cannabidiol	References
Beam test 5% ethanolic KOH	Reddish violet, yellowish brown on acidification	Deep violet, yellow on acidification	*C. A.*, **6**, 1952 (1912). Wellcome, *Trop Res. Labs. Khortoum*, 4th Rept. (B), 25.
Duquenois test acetaldehyde, vanillin–HCl	Opaque blue after several minutes	Clear pale blue, deepening on standing	*J. Egypt. Med. Assoc.*, **21**, 224 (1938) [*C. A.*, **32**, 5993 (1938)].
Ghamrawy test *p*-dimethylaminobenzaldehyde	Deep red; on dilution with water changes to deep purple	Bright red; on dilution with water changes to bluish green	*J. Egypt. Med. Assoc.*, **20**, 193 (1937) [*C. A.*, **32**, 4724 (1938)].
Ethanolic $FeCl_3$	No color	No color	*Pharm. Acta Helv.*, **1**, 210 (1926) [*C. A.*, **21**, 2050 (1927)].
Millon's reagent	Red and precipitate in cold	Red and precipitate in cold	Same
Ammoniacal $AgNO_3$	Reduces slightly in cold, readily when hot	Very slight reduction in cold, slow reduction when hot	Same
Fehling's soln.	Reduces slowly in cold, readily when hot	Reduces very slowly when hot, no reduction in cold	Same
Formaldehyde–H_2SO_4	Dark brown	Very deep red	*The Analyst*, **36**, 540 (1911).[a]
Opianic acid–H_2SO_4	Bright red changing to brown	Bright red	*Ber.*, **20**, 874 (1887).[a]
Alloxan–H_2SO_4	Deep red changing to brown	Bright red	*Chem. Zentr.*, **73**, I, 631 (1902).[a]
Acetic acid	No color	No color	*Pharm. Acta Helv.*, **1**, 210 (1926).
H_2SO_4	Brown	Pale orange, fading to pale yellow	Same
Acetic anh.–H_2SO_4	Brown	Light brown	Same
$CHCl_3$–H_2SO_4	Brown in acid layer	Brilliant brown red in acid layer	Same
$Ca(OCl)_2$	Yellowish red	No reaction	*Ann.*, **68**, 95 (1848).[a]
$CHCl_3$–10% aq. KOH	Dark red in aqueous layer	Red in aqueous layer	*Z. anal. Chem.*, **56**, 286 (1917).[a]
$NaNO_2$–dil. H_2SO_4	No reaction	No reaction	*Ber.*, **7**, 248 (1874).[a]

[a] Tests have not previously been used on red oil. References are to the description of the tests on simply polyhydroxy benzenes.

sium carbonate resulted finally in formation of a dimethyl ether. Oxidation with permanganate in acetone gave *n*-caproic acid, which represents strong evidence for an *n*-amyl group in a phenolic ring. From these few facts alone, it may be concluded that one-half of the molecule of cannabidiol probably corresponds to the right-hand half of cannabinol (I). However, both hydroxyls are free in the cannabidiol so that the possibility of a pyran ring such as exists in cannabinol is excluded. On the assumption that the cannabidiol resembles cannabinol in entirety, the other half of the cannabidiol molecule may be postulated as a partially hydrogenated methylisopropylbenzene nucleus. Thus, formula II expresses satisfactorily the available experimental facts.

If the correct formula is $C_{21}H_{30}O_2$ (II), then two double bonds or the equivalent must be present. The positions assigned them in II are essentially fortuitous as no sound evidence has yet been revealed whereby to place them. The possibility of one double bond and a three-, four-, or five-membered ring, such as occurs in many terpenes, is not excluded. On the other hand, if the formula of cannabidiol is $C_{21}H_{32}O_2$, only one double bond in the left-hand ring can be present. The analyses of cannabidiol and its derivatives, the esters and ether, do not make possible a definite conclusion about the formula though $C_{21}H_{30}O_2$ agrees somewhat more uniformly with the analyses and, therefore, appears the more likely. Hydrogenation experiments, which should lead to the detection of one or two double bonds, have as yet proven indecisive. It is hoped, however, that a



II

careful reduction study now under way may clarify the question of unsaturation.

Red oil probably contains other products closely related to cannabinol or cannabidiol in structure, such as partially hydrogenated cannabinols, isomers of cannabidiol, or molecules like cannabidiol with less unsaturation. A large number of closely related compounds is possible. The active marihuana principle or principles may be among this group of substances. On the other hand, the possibility of the presence in red oil of a very potent active compound, entirely unrelated structurally to cannabinol or cannabidiol, is not excluded.

Experimental

The hemp used in these experiments grew wild in Minnesota during the season of 1938. It was cut in August, after flowering had begun but before seed had "set" in the female tops. It was stored for six weeks in a room where a fan assured circulation of air in order to dry it completely. No molding occurred. The material was then beaten and shaken to remove the coarse stems which amounted to about one-third of the total dry weight. The stems were discarded and the relatively fine material that remained was extracted with 95% ethanol in the manner described below.

Four 20-gallon (75-liter) crocks, each holding approximately 23 lb. (10 kg.) of material, were set up in series for countercurrent extraction. Each crock held approximately 61 liters of solvent of which about 41 liters were withdrawn at each transfer, the remainder being retained by the hemp. Once the process had become uniform in operation, the extract received from crock no. 4 at each transfer reached a concentration of approximately 2 g. per 100 cc. Transfers were made once or twice a day as conditions warranted. The most concentrated extract thus obtained was passed to a concentrator where most of the solvent was "flashed off" under vacuum. It was never heated above 50°. The evaporation was carried out at about 30°. The concentrated solution contained in this case 23.1 g. of solids per 100 cc. and 1 cc. was equivalent to 4.13 g. of hemp extracted. The operations just described were carried out by Dr. John R. Matchett and his assistants in the Narcotics Laboratory of the Treasury Department, Washington, D. C. They kindly furnished us with a generous supply of ethanol extract.

The red oil from these extracts was obtained as follows. Into a 1-liter Claisen flask, with a wide short neck, filled with glass wool was poured ethanolic extract until two-thirds full. The bath temperature was raised gradually from 90–140° while the pressure was diminished slightly. The ethanol distillate was discarded and the flask again filled to two-thirds capacity. This process was repeated until a maximum of 1600 cc. of extract had been added and all the ethanol was distilled. The temperature was then gradually raised to 200° and when distillation of the last traces of ethanol ceased, the bath was lowered to 180° and the pressure gradually reduced to 30 mm. Great care was necessary to prevent the liquid from foaming over. The temperature was gradually raised to 200° (30 mm.) until distillation ceased. The bath was then cooled to 170° and the pressure reduced to 2–5 mm. The residual product was then distilled. Considerable care was necessary to keep the bath at the lowest temperature at which the oil distilled regularly since there was a particular tendency to foam when the superheating was excessive. The material distilled between 100–220° (3 mm.) with the bath temperature at 170–310°; yield 180–200 g.

This crude red oil was dissolved in 500 cc. of petroleum ether (b. p. 30–60°) and extracted twice with water. The aqueous extract was saved and worked up for water-soluble materials. The petroleum ether layer was distilled and the residue fractionated through a good column with an outside heating unit. The first fraction boiled at 115–150° (2 mm.) (bath temperature 190–210°); yield, 70–80 g. The second fraction boiled at 150–175° (2 mm.) (bath temperature 215–225°); yield 25–35 g. The residual material in the flask was removed while still hot by dissolving in ethanol and filtering from the glass wool. The ethanol was removed and the product distilled from a 250-cc. flask, b. p. 175–195° (2 mm.) (bath temperature 220–270°); yield 90–110 g. This last material was considered as purified red oil.

Cannabidiol *bis*-3,5-Dinitrobenzoate.—A solution of 50 g. of purified red oil, b. p. 175–195° (2 mm.), in 200 cc. of dry pyridine was poured rapidly with shaking and cooling on 85 g. of 3,5-dinitrobenzoyl chloride. The mixture was heated on a steam cone for two hours with occasional shaking and was then poured into ice and hydrochloric acid (200 cc. of concentrated hydrochloric acid, 500 cc. of ice). It was filtered or decanted and the insoluble material was washed several times with dilute hydrochloric acid. The residue was dissolved in 600 cc. of benzene and filtered. The insoluble material consisted mainly of 3,5-dinitrobenzoic acid.

The benzene solution was washed with dilute hydrochloric acid, then with aqueous sodium bicarbonate and finally with water. Considerable trouble was encountered with emulsions which broke with difficulty. The benzene was evaporated and the residue was dissolved in 500 cc. of dry ether. This solution was treated with norit (20 g.), filtered, and then concentrated to 300 cc. On cooling in an ice–salt mixture with constant stirring, crystallization set in. After one hour, the product was filtered and washed with cold dry ether. It was purified by recrystallizing from 800 cc. of a mixture of methanol and methyl acetate (2:1); white rods, m. p. 106–107° (corr.).

Anal. Calcd. for $C_{21}H_{28}(OCOC_6H_3(NO_2)_2)_2$: C, 59.82; H, 4.88; N, 7.97. Calcd. for $C_{21}H_{30}(OCOC_6H_3(NO_2)_2)_2$: C, 59.64; H, 5.15; N, 7.95. Found: C, 59.74; H, 5.00; N, 7.96. *Rotation.* 0.057 g. made up to 5 cc. with acetone at 27° gave α_D −1.73°; *l*, 2; $[\alpha]^{27}D$ −76°.

Cannabidiol.—A solution of 50 g. of cannabidiol *bis*-3,5-dinitrobenzoate in 100 cc. of toluene was placed in the glass liner of a high pressure bomb. The mixture was cooled by dry-ice and about 100 cc. of liquid ammonia passed into it. The liner was then placed in the bomb and the cover quickly fastened. The bomb was allowed to stand for five hours at room temperature. At the end of that time the excess ammonia was allowed to escape and the product, which had set to a solid mass, was digested with 400 cc.

of petroleum ether (b. p. 60–110°). The solid 3,5-dinitrobenzamide was filtered and washed with two 50-cc. portions of petroleum ether. Filtrate and washings were combined and extracted six times with 150-cc. portions of boiling water to remove the last traces of 3,5-dinitrobenzamide. The petroleum ether was then evaporated and the residue distilled, b. p. 187–190° (2 mm.) (bath temperature 220°), d^{40}_4 1.040; $n^{20}D$ 1.5404. Cannabidiol is a pale yellow resin; yield 17–19 g.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 80.08, 80.29; H, 9.87, 9.41. *Rotation.* 0.0378 g. made up to 5 cc. with 95% ethanol at 28° gave α_D −0.90°; *l*, 1; $[\alpha]^{28}D$ −119°.

A Zerewitinoff determination showed two active hydrogens.

Cannabidiol is soluble in all common organic solvents, ether, benzene, ethanol, methanol, chloroform, and petroleum ether, but insoluble in water and 10% hot or cold aqueous sodium hydroxide.

That no rearrangement or deep-seated decomposition had taken place by this method of hydrolysis was demonstrated by the fact that the product readily could be reconverted in essentially quantitative yields to the same *bis*-3,5-dinitrobenzoate.

Cannabidiol *bis*-*m*-Nitrobenzene Sulfonate.—To a solution of 0.2 g. of cannabidiol in 5 cc. of dry pyridine, 0.35 g. of *m*-nitrobenzene sulfonyl chloride was added. The mixture was warmed on a steam cone for one hour and was then poured into ice and hydrochloric acid. The product was filtered, washed with dilute hydrochloric acid, aqueous sodium bicarbonate and then with water. It was purified by recrystallization from ethanol: white rods, m. p. 119–120° (corr.); yield 0.17 g. This same derivative could be obtained directly from purified red oil.

Anal. Calcd. for $C_{21}H_{28}(OSO_2C_6H_4NO_2)_2$: C, 57.87; H, 5.30; N, 4.09. Calcd. for $C_{21}H_{30}(OSO_2C_6H_4NO_2)_2$: C, 57.70; H, 5.58; N, 4.08. Found: C, 57.72; H, 5.49; N, 4.39.

Cannabidiol Dimethyl Ether.—A solution of 11.25 g. of cannabidiol in 75 cc. of acetone was refluxed for four hours with 12 g. of methyl iodide and 15 g. of anhydrous potassium carbonate. A deep purple color present at the beginning of the reaction had changed to a pale yellow at the end of this time.

The potassium carbonate was filtered, washed with ether, and the filtrate and washings combined. The solution becomes cloudy due to the precipitation of salts dissolved in the acetone. About 300 cc. more of ether was added and the mixture extracted with water. The solvent was then removed and the product distilled. Five cuts of approximately equal volume were taken since temperature changes were not significant. The refractive indices of these fractions ranged from 1.5330 to 1.5372, indicating that some reaction had taken place but that the product was not homogeneous.

The distillate was dissolved again in acetone, treated with excess methyl iodide and potassium carbonate and refluxed for periods of ten, twelve, forty-eight, and sixty hours. After each treatment the progress of the reaction was followed by the refractive index as described above. At the end of a total of one hundred and thirty-four hours of refluxing the refractive index of the main portion of the distillate was found to have reached a constant value. The material thus obtained was a pale yellow oil, much less viscous than cannabidiol; b. p. 175–177° (3 mm.) (bath temperature 200°); yield 3.3 g.; $n^{20}D$ 1.5254; d^{20}_4 0.9823.

Anal. Calcd. for $C_{21}H_{28}(OCH_3)_2$: C, 80.65; H, 10.01; OCH_3, 18.12. Calcd. for $C_{21}H_{30}(OCH_3)_2$: C, 80.17; H, 10.53; OCH_3, 18.02. Found: C, 80.52; H, 10.08; OCH_3, 18.2. *Rotation.* 0.0535 g. made up to 5 cc. with 95% ethanol at 28° gave α_D −1.42°; *l*, 1; $[\alpha]^{28}D$ −133°.

Cannabidiol dimethyl ether is insoluble in water, difficultly soluble in cold 95% ethanol, and readily soluble in petroleum ether, acetone, and ether.

An attempt was made to prepare the monomethyl ether by refluxing cannabidiol in acetone solution for eight hours with over twice the theoretical amounts of methyl iodide and potassium carbonate. The product was worked up as described above and carefully fractionated. That portion of the distillate which seemed, on the basis of refractive indices, to be homogeneous was found to give a very satisfactory value for methoxyl content, but a consistently poor value for carbon. The material was a clear viscous oil, b. p. 177–179° (2 mm.) (bath temperature 200–210°); $n^{20}D$ 1.5311.

Anal. Calcd. for $C_{21}H_{29}O(OCH_3)$: C, 80.44; H, 9.82; OCH_3, 9.45. Calcd. for $C_{21}H_{31}O(OCH_3)$: C, 79.94; H, 10.37; OCH_3, 9.39. Found: C, 79.67, 79.50; H, 9.65, 9.79; OCH_3, 9.41. *Rotation.* 0.0455 g. made up to 5 cc. with 95% ethanol at 26° gave α_D −2.14; *l*, 2; $[\alpha]^{26}D$ −118°.

Oxidation of Cannabidiol.—To a solution of 5 g. of cannabidiol in 25 cc. of acetone was added a saturated solution of 8 g. of potassium permanganate in 50% aqueous acetone and 5 g. of sodium bicarbonate. The mixture was heated for thirty minutes on a steam-bath. Ethanol was added to remove the last traces of the permanganate, the mixture filtered and acidified with hydrochloric acid. The acid solution was extracted with ether and the ether solution in turn extracted with aqueous sodium bicarbonate.

The aqueous sodium bicarbonate solution was acidified with hydrochloric acid and extracted with ether. The ether solution was dried over anhydrous magnesium sulfate, the solvent removed and the product distilled. It boiled at 200–203° (750 mm.) and weighed 1.15 g. (64% based on one molecule of *n*-caproic acid per molecule of cannabidiol). The anilide was prepared for identification purposes, m. p. 95–96°, and proved to be identical with an authentic sample of *n*-caproanilide.

Summary

A new compound, cannabidiol, present in the purified red oil of *Cannabis sativa* has been isolated through the *bis*-3,5-dinitrobenzoate. This diester is a crystalline, easily purified compound. Ammonolysis of it gives cannabidiol which has the formula $C_{21}H_{30}O_2$ or $C_{21}H_{32}O_2$, the former probably being the correct one.

Cannabidiol is oxidized to *n*-caproic acid, methylated with difficulty to a dimethyl ether and

converted to a *bis-m*-nitrobenzenesulfonate. It is concluded that this substance is closely related to cannabinol in structure. Half the molecule is probably a dihydroxy *n*-amylphenyl, the other half probably an unsaturated alicylic nucleus.

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, COLUMBIA UNIVERSITY]

The Preparation and Properties of 3(α),11-Dihydroxy-12-ketocholanic Acid

BY BERNARD B. LONGWELL[1] AND O. WINTERSTEINER

The isolation of naturally occurring steroids in which an oxygen atom is believed to occupy position 11[2,3,4] renders of interest the study of model substances in which ring C carries a functional group in this, and only in this, position.

The original aim of this investigation was to prepare 3,11-dihydroxycholanic acid by elimination of the keto group of 3,11-dihydroxy-12-ketocholanic acid, which has been described recently by Marker and Lawson.[5] Although this object has not been accomplished, we are reporting here the preparation and properties of the starting compound because our results not only extend but in some points fail to confirm the work of these authors. Their procedure is essentially analogous to that of Wieland and Posternak[6] for the preparation of 11-hydroxy-12-ketocholanic acid. They[5] acetylated 3-hydroxy-12-ketocholanic acid, and then brominated it in position 11. The bromo acid was hydrolyzed to 3,11-dihydroxy-12-ketocholanic acid. Neither of the two intermediates was isolated. In our hands this abbreviated procedure failed to yield the end-product in crystalline form. We found it necessary to conduct the reaction in two separate steps. We furthermore had to modify the method of bromination in order to limit the reaction to a substitution with only one bromine atom. Although the bromo acid thus obtained was amorphous and its bromine content still slightly too high, its hydrolysis yielded the desired 3,11-dihydroxy-12-ketocholanic acid without any difficulty. The over-all yield from 3-hydroxy-12-ketocholanic acid was over 50%, whereas Marker and Lawson obtained in 35% yield a product which melted 9° lower than ours.

In order to eliminate any doubt regarding the site of the new hydroxyl group, the monobromo acid was subjected to debromination with anhydrous sodium acetate in analogy to the experiment of Barnett and Reichstein[7] on 11-bromo-12-ketocholanic acid. The ultraviolet absorption spectrum of the resulting compound (m. p. 201°) exhibited a maximum at 241 mμ (ϵ = 9000, solvent alcohol), which is characteristic for α,β-unsaturated ketones. The unsaturated compound is, therefore, $\Delta^{9,11}$-3-acetoxy-12-ketocholenic acid. Furthermore, the acid 3-succinate of methyl 3,11-dihydroxy-12-ketocholanate was oxidized with chromic acid to the corresponding 11,12-diketone. The ultraviolet absorption spectrum of the resulting compound is similar to that reported by Barnett and Reichstein for methyl 11,12-diketocholanate (maximum at 284 mμ, ϵ = 135; minimum at 250 mμ, ϵ = 80, solvent alcohol). Saponification of the diketo ester failed to yield a crystalline compound.

When we tried to repeat the preparation of the 3-monoacetate of 3,11-dihydroxy-12-ketocholanic acid described by Marker and Lawson, we observed that the reaction takes a more complicated course than the report of these authors indicates. Our acetylation product showed the same melting point (268°) as their monoacetyl derivative, but the analysis indicated the loss of a molecule of water as well as the esterification of one hydroxyl group. We are unable to explain the considerable discrepancy between the carbon value of our analyses and that reported by Marker and Lawson, but it must be pointed out that the values assigned in their paper to the monoacetyl acid, $C_{26}H_{40}O_6$, with which their experimental figures agree, are incorrectly calculated (C, 70.5; H, 8.8, instead of C, 69.60; H, 8.99). Furthermore, our substance, in contradistinction to the starting compound, is insoluble in aqueous sodium carbonate. Hydrolysis at room temperature

(1) Commonwealth Fund Fellow, 1938–1939.

(2) Reichstein, *Ergeb. der Vitamin- und Hormonforschung*, **1**, 334 (1938).

(3) Marker, Kamm, Crooks, Oakwood, Wittle and Lawson, THIS JOURNAL, **60**, 210 (1938).

(4) Tschesche and Bohle, *Ber.*, **69**, 793, 2497 (1936).

(5) Marker and Lawson, THIS JOURNAL, **60**, 1334 (1938).

(6) Wieland and Posternak, *Z. physiol. Chem.*, **197**, 17 (1931).

(7) Barnett and Reichstein, *Helv. Chim. Acta*, **21**, 926 (1938).