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Isolation of Cannabinol, Cannabidiol and Quebrachitol from Red Oil of Minnesota Wild Hemp

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The isolation of cannabidiol through its *bis*-3,5-dinitrobenzoate from the marihuana red oil of Minnesota wild hemp was described previously.[2] Since that time it has also been isolated from North African charas by Todd.[3] The procedure for obtaining cannabidiol through the ester has now been improved to the point where 45–50% of the purified red oil can be shown to be cannabidiol.

The changes consist mainly in a preliminary steam distillation, followed by a careful high vacuum distillation, which greatly facilitates isolation of a pure product, followed by prompt conversion to the *bis*-dinitrobenzoate. The details are given in the experimental part. The cannabidiol, through ammonolysis of the ester, has now been obtained in crystalline form as long, white rods from petroleum ether, m. p. 66–67°, $[\alpha]^{27}\mathrm{D}$ $-125°$. It was described previously[2] as an oil, b. p. 187–190° (2 mm.), $[\alpha]^{28}\mathrm{D}$ $-119°$.

Advantage has been taken of the chemical properties of cannabidiol to attempt a chemical method of separation of various constituents of red oil. Red oil was first treated for removal of cannabidiol as previously described.[2a] The filtrate from the cannabidiol *bis*-3,5-dinitrobenzoate was ammonolyzed to decompose any esters present and the residual oil (B) distilled. It was then pyrolyzed with pyridine hydrochloride at about 75–100 mm. pressure and 225–230° to convert any cannabidiol still present to cymene and olivetol.[2c] The cymene distilled and the mixture was then extracted with cold aqueous alkali. This removed about 10–15% of product (C). The alkali-insoluble portion (D) was distilled *in vacuo* and then treated in petroleum ether solution with 3,5-dinitrobenzazide.[4] Upon refluxing, a copious precipitate of urethans separated (E). The solid was crystallized from benzene, during which process a considerable loss occurred, possibly indicating the presence of a more soluble urethan (F). The less soluble urethan (G), $C_{21}H_{25}O{\cdot}OCONHC_6H_3(NO_2)_2$, after purification, was decomposed with ethanolic ammonia. The dinitrophenyl urea was insoluble and thus removed. The oil obtained by evaporation of the solvent (I) was distilled *in vacuo* and proved to have the boiling point of cannabinol. Upon cooling and scratching, the oil solidified and was recrystallized readily from petroleum ether. This product was indeed cannabinol, isolated for the first time in a crystalline state. It formed plates that were apparently monoclinic pseudohexagonal in form, m. p. 75–76°. Its derivatives proved to be identical with those from cannabinol previously obtained as an oil. The constants of pure crystalline cannabinol and derivatives made from it are given in Table I.

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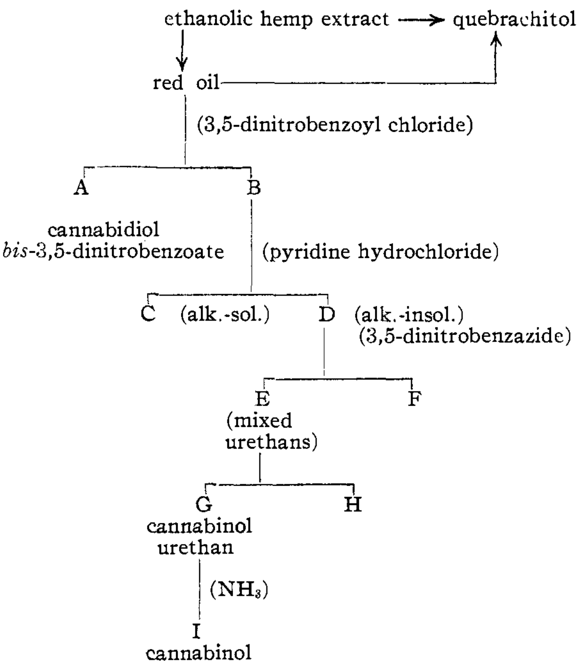

If any cannabidiol was carried over through this process without decomposition, it did not interfere with the crystallization of the dinitrophenyl urethan of the cannabinol present.

If purified red oil was pyrolyzed directly with pyridine hydrochloride to destroy the cannabidiol

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

[2] (a) Adams, Hunt and Clark, THIS JOURNAL, **62**, 196 (1940); (b) Adams, Cain and Wolff, *ibid.*, **62**, 732 (1940); (c) Adams, Hunt and Clark, *ibid.*, **62**, 735 (1940).

[3] Jacob and Todd, *Nature*, **145**, 350 (1940).

[4] Sah and Ma, *J. Chinese Chem. Soc.*, **2**, 41, 162 (1934).

TABLE I

CONSTANTS OF CANNABINOL AND DERIVATIVES[5]

	M. p., °C. (cor.)	Previously recorded M. p., °C.
Cannabinol	75–76	...
p-Nitrobenzoate	165–166	160[6]
m-Nitrobenzene sulfonate	127–129	125–126[7]
Acetate	76–77	75[8]

the product could also be separated into alkali-soluble and alkali-insoluble fractions. The removal of cannabinol from the alkali-insoluble fraction as the dinitrophenyl urethan was not as clean-cut as when cannabidiol was first removed from red oil.

In the isolation of pure red oil from crude ethanolic hemp extract, several distillations are necessary. Whenever the red oil was fractionated there deposited in the upper part of the Widmer column a small amount of crystalline material. This proved to be water-soluble. It was found that this same substance could be extracted from a petroleum ether solution of crude red oil by means of water and was also present in the aqueous layer after steam distillation of the hemp extract. It proved to be quebrachitol, the monomethyl ether of *l*-inositol, as shown by its physical and chemical properties and analysis, as well as by the characteristics of its pentaacetate.

The other fractions (C, F and H) in the schematic procedure just described for separating various products from red oil are being investigated. A somewhat similar method is being applied to "purified red oil" omitting the removal of cannabidiol as the 3,5-dinitrobenzoate. Attempts are under way to separate chemically the products from Indian charas following the procedure described.

Experimental

Purified Red Oil.—The ethanol from 4 liters of ethanolic hemp extracts[2a] (25% solids) was removed by distillation. The residue was subjected to steam distillation to remove terpenes; after the collection of about 8 liters of distillate, the distillation was assumed to be complete. The water-insoluble residue was separated from the water, dissolved in petroleum ether (b. p. 30–60°) and the solution extracted three times with water. After evaporation of the solvent, the oil was distilled, b. p. 70–160° (5×10^{-3} mm.), with the temperature of the still varying from 180–250°. Care was taken in this and subsequent distillations to stop the distillation the moment gases appeared through the apparatus, indicating decomposition. About 300 g. of crude red oil resulted. This was dissolved in petroleum ether, washed with water, the solvent removed and again distilled through a heated carborundum-filled column (35 cm. long with outside diameter of column 23 mm. and of side-arm 12 mm.). Two fractions, about 30 g. each, were separated, one b. p. 70–130°, the second b. p. 130–150° (5×10^{-3} mm.) from which solid material crystallized on cooling (probably nonacosane). When all of the distillate from which solid crystallized had been removed, the fractionating column was replaced by a still head with side-arm of 15 mm. diameter and the material, b. p. 148–160° (5×10^{-3} mm.) (still temp. 180–230°), was collected. It was a clear, light red viscous oil weighing 200 g. and will be designated as "purified red oil."

Cannabidiol *bis*-3,5-Dinitrobenzoate.—Immediately after the purified red oil had been distilled, a solution of 185 g. in 300 cc. of pyridine cooled to 0° was combined with a solution of 250 g. of 3,5-dinitrobenzoyl chloride in 400 cc. of warm pyridine which was then cooled to 0° before the addition. The mixture was well stirred and the lumps broken up while standing in ice for thirty minutes. It was then warmed on a steam-bath for thirty minutes with stirring to disintegrate all lumps. The temperature of the mixture rose to about 60° and its color deepened somewhat. The reaction mixture was then treated immediately with ice and 10% sulfuric acid. The ester was taken up in benzene, washed with 5% sulfuric acid, then aqueous sodium bicarbonate. The benzene was completely removed on a water-bath and ether was added in volume about equal to that of the product. On standing and seeding, crystalline cannabidiol *bis*-3,5-dinitrobenzoate separated and was increased in amount by cooling in an ice–salt-bath; yield of dry crude ester, 195 g. (47%). The procedure for purification and melting point have been given in another communication.[2a]

Crystalline Cannabidiol.—A few drops of cannabidiol, prepared from purified *bis*-dinitrobenzoate as described previously,[2a] was allowed to stand for several weeks spread in a thin layer on glass, after which time it crystallized spontaneously. Using the seed crystals obtained in this way oily cannabidiol was crystallized readily. Recrystallization from petroleum ether (b. p. 30–60°) gave long white rods, m. p. 66–67° (cor.).

Rotation. 0.0665 g. made up to 5 cc. with 95% ethanol at 27° gave α_D −1.66°; *l*, 1; $[\alpha]^{27}_D$ −125°.

Crystalline cannabidiol was converted to the *bis*-3,5-dinitrobenzoate which was identical in melting point and mixed melting point with that obtained from the oily form.

3,5-Dinitrophenyl Urethan of Cannabinol from Red Oil.—The filtrates from the crude precipitate of cannabidio-*bis*-3,5-dinitrobenzoate were evaporated to free from solvent and dissolved in toluene. The solution was then all lowed to stand with liquid ammonia in a bomb for eight hours. The dinitrobenzamide which separated was filtered, the toluene distilled, the residue taken up in petroleum ether (b. p. 60–110°) and extracted with hot water. The material in the petroleum ether distilled in a

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[5] Samples of cannabinol acetate and *p*-nitrobenzoate were submitted to us by Dr. A. R. Todd of the University of Manchester to whom we desire to express our thanks. Mixed melting points of his products and those prepared in this research showed no depression. Melting points previously reported by Todd for his compounds obviously had not been corrected values as these were found actually to be slightly above the ones reported and slightly lower than the corrected values of our compounds.

[6] Work, Bergel and Todd, *Biochem. J.*, **33**, 124 (1939).

[7] Cahn, *J. Chem. Soc.*, 1347 (1932).

[8] Wood, Spivey and Easterfield, *J. Chem. Soc.*, **75**, 20 (1899).

high vacuum at essentially the same point as purified red oil. It contained some nonacosane, ethyl 3,5-dinitrobenzoate and ethyl 3-amino-5-nitrobenzoate. Most of these impurities could be removed by taking up first in methanol and then in petroleum ether (b. p. 30–60°), followed by cooling and filtering in each case. The ethyl 3-amino-5-nitrobenzoate could be removed completely by extracting the petroleum ether solution with cold 20% hydrochloric acid. The oil then was redistilled in a high vacuum.

A mixture of 20 g. of the oil just described and 30 g. of dry pyridine hydrochloride was heated under 75–100 mm. pressure at 225–230° (bath temp.) for three hours. Provision was made to retain distillable substances in a dry-ice trap. A small amount of material, presumably *p*-cymene, was thus collected. The cooled reaction mixture was taken up in benzene and the benzene solution washed with water, twice with cold 10% aqueous sodium hydroxide, 5% hydrochloric acid, and finally with aqueous bicarbonate. The sodium hydroxide extract was retained for isolation of alkali-soluble products. The oil remaining in the benzene was then distilled, giving a light amber oil weighing 11 g. It gave no alkaline Beam test.

To a solution of 20 g. of the alkali-insoluble oil, obtained from the pyridine hydrochloride pyrolysis, in 300 cc. of petroleum ether (b. p. 60–110°) was added 18 g. of 3,5-dinitrobenzazide.[9] The reaction mixture was then heated to reflux for thirty minutes to one hour. At the end of this time, a light yellow solid had separated (about 20–25 g.). After cooling, it was filtered and recrystallized five times from benzene; yield 5 g., m. p. 220–222° with decomposition. The urethan was also obtained by condensation of crystalline cannabinol with 3,5-dinitrobenzazide. Two crystallizations gave a pure compound; light yellow needles, m. p. 221–222° with decomposition.

Anal. Calcd. for $C_{28}H_{29}O_7N_3$: C, 64.71; H, 5.63. Found: C, 65.05; H, 5.80.

Cannabinol.—A mixture of 7.5 g. of the 3,5-dinitrophenyl urethan of cannabinol (m. p. 220–222°) in 200 cc. of 95% ethanol and 12 g. of liquid ammonia was allowed to stand. As ammonolysis proceeded, the urethan went into solution and the solute became clear. After standing for three to four hours with occasional shaking, the ethanol was distilled. The residue was extracted with petroleum ether (b. p. 60–110°), the petroleum ether extract washed several times with hot water and the solvent evaporated. The product was completely soluble in petroleum ether (b. p. 30–60°). It was then distilled, b. p. 185° (0.05 mm.) (bath temp. 225–240°); yield 3 g. On scratching the distillate, the oil solidified and was purified by recrystallization from petroleum ether (b. p. 30–60°); plates that were apparently monoclinic pseudohexagonal in form, m. p. 75–76° (cor.).

Anal. Calcd. for $C_{21}H_{26}O_2$: C, 81.21; H, 8.45. Found: C, 81.44; H, 8.53.

Isolation of Quebrachitol (*l*-Inositol Monomethyl Ether).—The aqueous layer obtained after the steam distillation of the ethanolic hemp extract described above was partially defecated with basic lead acetate. The excess lead was removed by the addition of sulfuric acid, followed by hydrogen sulfide to remove the last traces. The water was evaporated and the thick brown oil obtained was distilled at a pressure of 2 mm. The product, a dark red oil, distilled slowly at a temperature of 190–220°. The distillate was dissolved in water, treated once with norit, and most of the water evaporated. Ethanol and acetone were added until the solution became cloudy. After two to three days a crystalline solid separated and was recrystallized from *n*-propanol; white granular crystals, m. p 192–193° (cor.).

Anal. Calcd. for $C_7H_{14}O_6$: C, 43.30; H, 7.27. Found: C, 43.17; H, 7.18. *Rotation.* 0.2280 g. made up to 5 cc. with water at 25° gave α_D $-3.67°$; *l*, 1; $[\alpha]^{25}_D$ $-80.5°$.

The melting point and rotation of the compound agreed quite closely with the values reported previously for quebrachitol.[10]

A small additional amount of quebrachitol was isolated from the extraction with water of a petroleum ether solution of red oil after the first vacuum distillation. It was also obtained from the water extraction step in the preparation of red oil by the method described previously.[2a]

Quebrachitol Pentaacetate.—Prepared as previously described[11] it formed white crystals from chloroform; m. p. 96–97° (cor.). Contardi reported m. p. 91°.

Anal. Calcd. for $C_{17}H_{24}O_{11}$: C, 50.49; H, 5.98. Found: C, 50.30; H, 5.81. *Rotation.* 0.2072 g. made up to 5 cc. with chloroform at 29° gave α_D $-2.08°$; *l*, 2; α^{29}_D $-25.1°$.

Summary

1. Crystalline cannabidiol has been described for the first time.

2. A procedure for isolating cannabinol from red oil of Minnesota wild hemp is given. It was isolated through the 3,5-dinitrophenyl urethan from cannabidiol-free red oil. Cannabinol was obtained crystalline.

3. From red oil by distillation or by water extraction of crude red oil, or from the aqueous layer after steam distillation of the hemp extract, quebrachitol was isolated.

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[9] The product was prepared as described by Sah and Ma[4] except that the azide was allowed to crystallize from the acetic acid instead of precipitating with water. In this way a purer product was obtained. m. p. 100–103° (cor.) with decomposition. Sah reported 87–89°.

[10] De Jong, *Rec. trav. chim.*, **25**, 48 (1906), m. p. 190–191°, $[\alpha]^{28}_D$ $-80.2°$; Clark, THIS JOURNAL, **58**, 1009 (1936), m. p. 192–193° (cor.), $[\alpha]^{26}_D$ $-81.2°$; Bourquelot and Hérissey, *Compt. rend.*, **168**, 414 (1918), m. p. 190°, $[\alpha]_D$ $-80.6°$; Tanret, *ibid.*, **109**, 908 (1889), m. p. 186–187°.

[11] Contardi, *Ann. chim. applicata*, **14**, 281 (1924); *C. A.*, **19**, 1135 (1925).