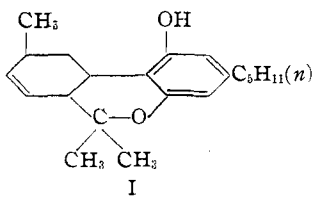
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, AND FROM THE DEPARTMENT OF PHARMACOLOGY, CORNELL UNIVERSITY MEDICAL COLLEGE, IN COLLABORATION WITH THE TREASURY DEPARTMENT, NARCOTICS LABORATORY, WASHINGTON, D. C.]

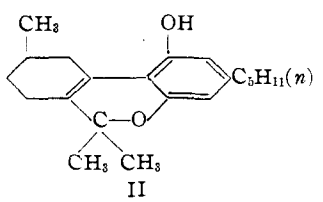
Optically Active Synthetic Tetrahydrocannabinols; *d*- and *l*-1-Hydroxy-3-*n*-amyl-6,9,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyrans. XIV[1]

BY ROGER ADAMS, C. M. SMITH AND S. LOEWE

The tetrahydrocannabinol resulting from the isomerization of cannabidiol has been postulated as having structure I and is optically[2] active. A synthetic, racemic tetrahydrocannabinol obtained by the condensation of ethyl 5-methylcyclohexanone-2-carboxylate with olivetol, followed by treatment of the resulting pyrone with excess methylmagnesium iodide has the formula II.[3]



I



II

Compound II has about one-seventh the potency of I, which was derived from a natural source.

This investigation was undertaken to prepare the optically active forms of II and to compare them in physiological activity. Optically active *d*- and *l*-3-methylcyclohexanone were obtained and subjected to the same series of reactions previously used for converting the *dl*-modification to *dl*-tetrahydrocannabinol. Pulegone, upon hydrolysis according to the procedure of Wallach,[4] yielded *d*-3-methylcyclohexanone in what appears to be optical purity. The *l*-form is much less accessible and was finally obtained by the resolution of the *dl*-form through the 1-menthydrazone.[5] The less soluble menthydrazone was the *l,l*-modification, which was readily hydrolyzed to *l*-3-methylcyclohexanone of rotation only slightly lower than that observed for the *d*-form from pulegone. The intermediates in the preparation of the tetrahydrocannabinols derived from the *d*- and *l*-3-methylcyclohexanones showed essentially parallel rotations, but the final products differed considerably. The *l*-pyran happened to be a little more highly colored than usual and was decolorized by refluxing in ethanol with activated charcoal for a longer period than was used in the case of the *d*-form. This apparent racemization was checked using a sample of the *d*-pyran, $[\alpha]^{25}D$ +147° in ethanol. After prolonged refluxing in ethanol with activated charcoal, this substance had $[\alpha]^{28}D$ +123°. It is not improbable that either disproportionation or an actual dehydrogenation may take place. Assuming the *d*-tetrahydrocannabinol to be optically pure, the *l*-modification finally obtained was 87% pure.

Pharmacological tests revealed that the *d*-form is about 40% as active as the racemic and that the *l*-form has between four and five times the physiological potency of the *d*-form. The precise results are shown in Table I.

TABLE I

POTENCY OF OPTICALLY ACTIVE TETRAHYDROCANNABINOLS[a]

	Number of expts.	Potency	Range of variation
dextro-Pyran (II) $[\alpha]^{20}D$ +155	11	0.38	±0.025
levo-Pyran (II) $[\alpha]^{26}D$ −114	9	1.66	± .21

[a] *dl*-Tetrahydrocannabinol was used as standard.

It is pertinent that both the tetrahydrocannabinol (I) from cannabidiol and the purified active fractions from red oil of hemp are[6,7] levorotatory.

Before this investigation was complete, Leaf, Todd and Wilkinson[8] published a description of the *d*-form of the tetrahydrocannabinol (II), made in essentially the same way as herein reported. On the basis of their pharmacological results, using the Gayer test, they estimate the *d*-form to be one-sixth to one-eighth as active as the racemic modification. This discrepancy in their results and ours (about one-third the potency) lies prob-

(1) For previous paper see Adams, Loewe, Smith and McPhee, THIS JOURNAL, **64**, 694 (1942).

(2) Adams, Loewe, Pease, Cain, Wearn, Baker and Wolff, *ibid.*, **62**, 2566 (1940).

(3) Adams and Baker, *ibid.*, **62**, 2405 (1940).

(4) Wallach, *Ann.*, **289**, 340 (1896).

(5) Woodward, Kohman and Harris, THIS JOURNAL, **63**, 122 (1941).

(6) Adams, Pease, Cain and Clark, *ibid.*, **62**, 2402 (1940).

(7) Wollner, Matchett, Levine and Loewe, *ibid.*, **64**, 26 (1942).

(8) Leaf, Todd and Wilkinson, *J. Chem. Soc.*, 185 (1942).

ably in the method of testing. The Gayer test used by these investigators, in our hands, has been much less quantitative and less reliable an index of potency than the dog-ataxia method used by us for determining the activity of these substances.

In this recent paper of Leaf, Todd and Wilkinson, exception is taken to a previous statement made by us[9] that migration of a double bond from conjugation with a benzene nucleus is without precedent. They consider this statement ill-advised in view of the numerous cases of deconjugation in the literature. They cite as references merely well-known cases of deconjugation in the terpene series which can hardly be considered refutatory to our statement about molecules of the type under consideration, where the double bond is conjugated to a benzene ring and no other group is present in the molecule to which the double bond might conjugate preferably.

Experimental

***d*-3-Methylcyclohexanone.**—The details for the preparation of this product from pulegone are described since Wallach gave none.

From 200 g. of pulegone and 160 cc. of water, heated at 250° for six hours, an organic layer was obtained which was shaken with saturated aqueous sodium bisulfite until solidification occurred. The cake was broken up, about one-third of its volume of ether added, and the whole was shaken, water being added gradually until the bisulfite compound just dissolved. Treatment of the aqueous layer with one-half its volume of saturated sodium carbonate solution yielded 39 g. of *d*-3-methylcyclohexanone or 26.5% of the theoretical. The constants observed were b. p. 164–168°; $n^{20}D$ 1.4445; d^{20}_4 0.9179.

Rotation. $\alpha^{20}D$ +12.21° (pure liquid); *l*, 1; $[\alpha]^{20}D$ +13.3°. Wallach reported $[\alpha]^{15}D$ +13.38°.

The semicarbazone purified from ethanol had a m. p. 181° (cor.); Wallach reported 180°.

Rotation. 0.3625 g. made up to 25 cc. with ethanol at 20° gave αD −0.60°; *l*, 2; $[\alpha]^{20}D$ −20.7°.

***d*-3-Methylcyclohexanone-*l*-menthydrazone.**—A mixture of 1.5 g. of *d*-3-methylcyclohexanone, 3.0 g. of l-menthydrazide, 0.2 g. of sodium acetate, 0.1 cc. of acetic acid and 20 cc. of ethanol was refluxed for two hours, diluted with water and the product allowed to crystallize. It was purified from 50% ethanol; white needles, softening at 126–130° and melting at 130–136° (cor.).

Anal. Calcd. for $C_{18}H_{32}O_2N_2$: C, 70.06; H, 10.46. Found: C, 70.00; H, 10.39.

Rotation. 0.2700 g. made up to 5 cc. with ethanol at 25° gave αD −3.31°; *l*, 1; $[\alpha]^{25}D$ −61.3°. The product from the mother liquors from the last crystallization gave the same rotation.

***l*-3-Methylcyclohexanone.**—By following the procedure just described, 162 g. of *dl*-3-methylcyclohexanone and 310 g. of *l*-menthydrazide in 400 cc. of ethanol gave a product which after filtering and recrystallizing from 1800 cc. of 65% ethanol, amounted to 195 g. This was recrystallized several times from the same solvent, then repeatedly from petroleum ether (b. p. 60–110°). When much of the more soluble derivative was present, the latter solvent could not be used as the substance tends to separate as a gel. It was found desirable not to heat the compound too much in the solvent and to remove the solvent under diminished pressure. After twenty crystallizations, there was obtained 13 g. of product of very nearly constant rotation, m. p. 146° (cor.).

Anal. Calcd. for $C_{18}H_{32}O_2N_2$: C, 70.06; H, 10.46. Found: C, 70.18; H, 10.94.

Rotation. 0.298 g. made up to 5 cc. with ethanol at 25° gave αD −1.90°; *l*, 1; $[\alpha]^{25}_4$ −31.3°.

Hydrolysis by warming with 10% sulfuric acid followed by steam distillation gave 3.7 g. of ketone; b. p. 164–168°; $n^{20}D$ 1.4449; d^{20}_4 0.9133; d^{25}_4 0.9108.

Anal. Calcd. for $C_7H_{12}O$: C, 74.94; H, 10.79. Found: C, 74.84; H, 10.69.

Rotation. $\alpha^{20}D$ −11.54° (pure liquid); *l*, 1; $[\alpha]^{20}D$ −12.64°.

The semicarbazone, purified from ethanol, melted at 181° (cor.).

Rotation. 0.1154 g. made up to 10 cc. with ethanol at 27° gave αD +0.24°, *l*, 1; $[\alpha]^{27}D$ +20.8°.

***d*- and *l*-Ethyl 5-Methylcyclohexanone-2-carboxylate.**—A solution of 5.95 g. of sodium in 120 cc. of absolute ethanol was cooled to 3° in an ice-bath and with stirring a mixture of 29 g. of *d*- or *l*-3-methylcyclohexanone and 38 g. of pure ethyl oxalate was added gradually. The temperature was maintained at 3–5° during the addition and for an hour thereafter. After standing overnight at room temperature, the reaction mixture was hydrolyzed by pouring onto a mixture of 15 cc. of sulfuric acid and cracked ice. The pale yellow oil was separated and the aqueous solution extracted with chloroform. The combined oil and extracts were washed with water plus a little sodium bicarbonate solution until neutral to congo red, dried and distilled in the presence of powdered soft glass and a trace of iron powder.

The *d*-product boiling at 100–140° (24–28 mm.) was collected and fractionated. The large middle fraction, b. p. 122–124° (15 mm.) was colorless, weighed 29 g. (61%) and had $n^{20}D$ 1.4722; d^{20}_4 1.040.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.18; H, 8.76. Found: C, 64.93; H, 8.68.

Rotation. $\alpha^{20}D$ +94.4° (pure liquid); *l*, 1; $[\alpha]^{20}D$ +90.8°.

After standing two months, this material had $[\alpha]^{28}D$ +73°. This decrease in rotation was probably due to re-establishment of the keto–enol equilibrium, since the value of +90.8° was obtained on freshly distilled material.

Gardner, Perkin and Watson[10] prepared the *d*-modification of this compound from an optically impure sample of *d*-3-methylcyclohexanone by carboxylation of the ketone with sodamide and carbon dioxide followed by esterification; they reported $[\alpha]D$ +84.2 in ethanol. Leaf, Todd and Wilkinson used a sample $[\alpha]^{19}D$ +79.2° (pure liquid).

(9) Adams, Smith and Loewe, THIS JOURNAL, **63**, 1973 (1941).

(10) Gardner, Perkin and Watson, *J. Chem. Soc.*, **97**, 1768 (1910).

Assuming the ester has a maximum rotation of +90.8°, this product corresponds to 93% purity.

The *l*-product was collected at 126–130° (17 mm.); $n^{20}D$ 1.4730; d^{20}_4 1.043.

Anal. Calcd. for $C_{19}H_{16}O_3$: C, 65.18; H, 8.76. Found: C, 65.41; H, 8.69.

Rotation. $\alpha^{20}D$ −88.26° (pure liquid); *l*, 1; $[\alpha]^{20}D$ −84.6°.

***d*- and *l*-1-Hydroxy-3-*n*-amyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone.**—These were prepared from the previously described *d*- and *l*-ethyl 5-methylcyclohexanone-2-carboxylates in a synthesis identical with that for the *dl*-modification.[8]

The *d*- and *l*-products were purified from methanol, m. p. 177° (cor.) in each case.

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.03. Found: (dextro form) C, 75.97; H, 7.98; (levo form) C, 76.17; H, 8.13.

Rotation. (*d*-form) 0.3936 g. made up to 25 cc. with ethanol at 28° gave αD +4.20°; *l*, 2; $[\alpha]^{27}D$ +133°. 0.0205 g. made up to 5 cc. with chloroform at 25° gave αD +0.56°; *l*, 1; $[\alpha]^{25}D$ +137°. Leaf, Todd and Wilkinson[8] gave $[\alpha]^{24}D$ +130.3° in chloroform. (*l*-form) 0.1214 g. made up to 25 cc. with ethanol at 27° gave αD −1.23°; *l*, 2; $[\alpha]^{27}D$ −127°.

***d*- and *l*-1-Hydroxy-3-*n*-amyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran.**—These were prepared from the optically active pyrones with rotations given above by use of excess methylmagnesium iodide as previously described for the *dl*-modification.

The *d*-form had a b. p. of 175–185° (0.1 mm.), bath temp. 205–210°; $n^{20}D$ 1.4550; the *l*-form had identical b. p. and index of refraction.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.20; H, 9.62. Found: (*d*-form) C, 80.01; H, 9.63. (*l*-form) C, 80.07; H, 9.67.

Rotation. (*d*-form) 0.1742 g. made up to 5 cc. with ethanol at 20° gave αD +5.41°; *l*, 1; $[\alpha]^{20}D$ +155°. 0.1456 g. of a sample which had $[\alpha]^{25}D$ +147° in ethanol, made up to 5 cc. with chloroform at 25° gave αD +4.32°; *l*, 1; $[\alpha]^{25}D$ +147.5°. Leaf, Todd and Wilkinson[8] report $[\alpha]^{20}D$ +134.8°. (*l*-form) 0.0873 made up to 5 cc. with ethanol at 26° gave αD −1.99°; *l*, 1; $[\alpha]^{26}D$ −114°.

Pharmacological Tests.—These were performed by the dog-ataxia method as described in previous papers.[7,11,12]

Summary

1. The *d*- and *l*-forms of 3-methylcyclohexanone have been synthesized; the former was prepared by hydrolysis of pulegone; the latter by resolution of the *dl*-methylcyclohexanone through the *l*-menthydrazone.

2. These were converted to the active ethyl 5-methyl-cyclohexanone-2-carboxylates, which were condensed with olivetol to form the *d*- and *l*-pyrones. By the action of excess methylmagnesium iodide, the *d*- and *l*-1-hydroxy-3-*n*-amyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyrans resulted.

3. The *l*-modification had four to five times the marihuana activity of the *d*-form.

(11) Loewe, *J. Pharm. Exper. Therap.*, **66**, 23 (1939); *J. Am. Pharm. Soc.*, **28**, 427 (1939).

(12) Matchett and Loewe, *ibid.*, **30**, 130 (1941).

URBANA, ILLINOIS RECEIVED JULY 6, 1942

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. CLI. Rearrangement of 17,21-Dibromo-*allo*-pregnan-3(β)-ol-20-one Acetate[1]

BY RUSSELL E. MARKER, HARRY M. CROOKS, JR., R. B. WAGNER AND EMERSON L. WITTBECKER

Recently,[2] we have shown that an equimolecular quantity of bromine with 20-keto-pregnane compounds introduces a bromine atom at C-17. Further bromination of these compounds substitutes a second bromine atom at C-21. Studies with these compounds have shown them to be particularly susceptible to rearrangement. The monobromo derivative[3] treated with methanolic potassium bicarbonate rearranges to place methyl and carbomethyoxyl groups at C-17. The 17,21-dibromo derivatives[2] under more vigorous alkali treatment yield Δ^{17-20}-pregnen-21-oic acids. The latter rearrangement products are particularly interesting since they can be degraded easily to the etio-cholane series. This fact has given support for their structure. We have now extended some of these reactions to *allo*-pregnan-3(β)-ol-20-one as a further study of the 17,21-dibromo-20-keto-pregnane rearrangement in the *allo* series.

allo-Pregnan-3(β)-ol-20-one or its acetate (I) with an equimolecular quantity of bromine readily forms a 17-monobromide (II) which can be reconverted to the parent compound or converted to 16-*allo*-pregnen-3(β)-ol-20-one by reactions described before.[2] In the same manner 17-bromo-

(1) Original manuscript received July 16, 1941.

(2) Marker and co-workers, THIS JOURNAL, **64**, 210, 213, 817, 822 (1942).

(3) Marker and Wagner, *ibid.*, **64**, 216, 1273 (1942).