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

# Structure of Cannabidiol. XII. Isomerization to Tetrahydrocannabinols[1]

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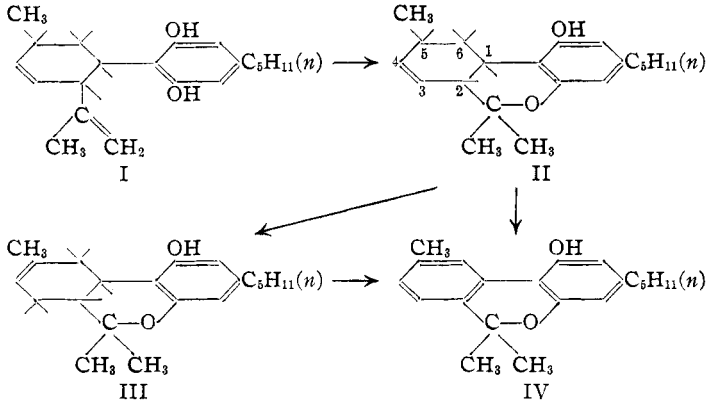
Crystalline cannabidiol (I) isomerizes readily in the presence of a number of acidic reagents to give a tetrahydrocannabinol (II or III).[3] The general structure of the latter was established by dehydrogenation to cannabinol (IV), a product




which was synthesized by two unequivocal methods. Dependent upon the conditions used, the tetrahydrocannabinol obtained had a specific rotation which was reported as $\alpha_D$ $-160 \pm 10°$ or $\alpha_D$ $-240 \pm 10°$. The results in preparing these forms were variable. Even though carefully controlled, successive experiments often gave products with different rotations.

The study of the isomerization of cannabidiol has been continued. It has now been found that very dilute ethanolic hydrochloric acid will convert cannabidiol to a tetrahydrocannabinol $\alpha_D$ $-130 \pm 5°$. An excellent new reagent for converting cannabidiol to high-rotating tetrahydrocannabinol $\alpha_D$ $-265 \pm 5°$ has been discovered in *p*-toluenesulfonic acid which is used in benzene solution and refluxed with the cannabidiol for one to two hours or longer. A drop of sulfuric acid (100%) in cyclohexane acts similarly. On the other hand, trichloroacetic, anhydrous oxalic, picric, 3,5-dinitrobenzoic, 87% formic, glacial acetic and maleic acids failed to isomerize cannabidiol, at least more than partially, in ten to twenty hours of boiling in benzene solution.

Unlike the previous conversions, these forms could be duplicated at will and it is believed that each represents an essentially pure product. It was reported previously that the reagents which convert cannabidiol to the high-rotating tetrahydrocannabinol also convert a low-rotating tetrahydrocannabinol to the same form. However, further experimentation has demonstrated that it is never possible to obtain by this latter conversion a product which has a rotation of $\alpha_D$ $-265 \pm 5°$. The maximum rotation ordinarily is within the range $\alpha_D$ $-200$ to $-225°$. This is true also of the tetrahydrocannabinol $\alpha_D$ $-130 \pm 5°$ described for the first time in this communication. The explanation of the discrepancy still is being sought but the reduction experiments lead to the belief that it may be accounted for possibly by the difficulty of complete conversion to a single product after the pyran ring once has been established. Upon reduction of a tetrahydrocannabinol of any rotation between $\alpha_D$ $-130°$ and $-270°$, there is always formed a homogeneous hexahydro product of constant rotation $\alpha_D$ $-70°$. The shifting of the nuclear double bond in the cannabidiol may take place simultaneously with or preceding the cyclization to the pyran.

It was suggested earlier[4] that since the reduction of tetrahydrocannabinols of varying rotation gave a hexahydrocannabinol of the same rotation, the difference in the rotation of the low- and high-rotating forms was due, probably, to the shifting of the double bond in the left-hand ring. The position of the double bond in the lower-rotating isomer was assigned that shown in II, since it was produced the more easily and since the evidence favors that position for the nuclear double bond in cannabidiol (I). The terminal double bond in cannabidiol was definitely established; the other

(1) For previous paper see Adams, Cain and Loewe, THIS JOURNAL, **63**, 1977 (1941).

(2) An abstract of a thesis submitted in partial fulfilment for the degree of Doctor of Philosophy in Chemistry.

(3) Adams, Pease, Cain and Clark, THIS JOURNAL, **62**, 2402 (1940).

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

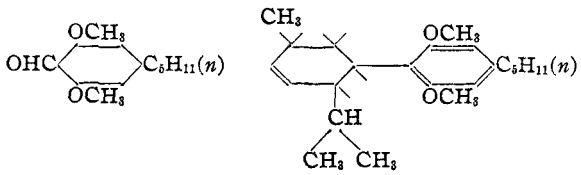
double bond was assigned the 3,4-position partly on the basis of absorption spectra.[5] These eliminated the possibility of a double bond conjugated with the benzene ring and rendered unlikely a conjugated system of double bonds in the left-hand ring. Failure of cannabidiol dimethyl ether to react with maleic anhydride confirmed this latter fact. The shift of a double bond in the 2,3- or 5,6-position of tetrahydrocannabinol by acidic reagents would, expectedly, take place to the 1,2- or 6,1-position, but experiments demonstrated that the product of reaction did not have a double bond conjugated to the benzene ring. The 3,4-position (II) for the double bond is, therefore, selected as the most likely for the low-rotating isomer, $\alpha_D$ −130°, and the 4,5-position (III) for the high-rotating form, $\alpha_D$ −265°.

Indication of a shift of a double bond in the tetrahydrocannabinols has been obtained through the observation that the tetrahydrocannabinol $\alpha_D$ −130° adds hydrogen chloride from an ether solution and gives an addition product (an oil) too unstable to purify, but undecomposed on shaking with dilute aqueous sodium bicarbonate. Upon distillation it loses hydrogen chloride with generation of a product $\alpha_D$ −203°. Attempts to replace the chlorine atom in the addition product by other groups failed.

It appears that the product $\alpha_D$ −160°, which varies so in rotation with minor changes in conditions of preparation, may be a mixture of the isomers $\alpha_D$ −130° and $\alpha_D$ −265°. No further experimental evidence is available to support this assumption. Various attempts to separate the form $\alpha_D$ −160° by chromatographic absorption into the lowest- and highest-rotating forms were unsuccessful. Similarly, the product $\alpha_D$ −225° to −240° is probably a mixture.

Further study was made of the position of the double bond in the left-hand ring of cannabidiol. Cannabidiol dimethyl ether was ozonized. After decomposing the ozonide in warm water, methone was added and the formaldehyde derivative isolated. This verified the terminal double bond previously determined by a color reaction. The other product or products were aldehydic oils which gave no solid derivatives and which oxidized to unidentifiable acids.

In one experiment, when the ozonide was decomposed with chromic acid in acetic acid, an oily product was obtained from which a small amount of a crystalline dinitrophenylhydrazone was isolated. This was derived from an aldehyde or ketone of formula $C_{14}H_{20}O_3$ which, probably, is the aldehyde of olivetol dimethyl ether (V).




V VI

Dihydrocannabidiol dimethyl ether (VI) also was studied with care. The usual reagents which add hydroxyls to the double bond, such as hydrogen peroxide in the presence of osmium tetroxide and monoperphthalic acid, failed to give solid glycol products. These latter on oxidation with lead tetraacetate or periodic acid gave only oils from which no solid derivatives could be isolated.

In an attempt to cause a shift in the double bond in the left-hand ring similar to that which occurred under the same conditions with low-rotating tetrahydrocannabinol, dihydrocannabidiol dimethyl ether was heated in benzene solution with *p*-toluenesulfonic acid. A change in rotation of the molecule was expected. Instead, a cleavage took place analogous to that which occurred when cannabidiol was heated with pyridine hydrochloride[6] to a relatively high temperature. The reaction mixture, upon distillation, yielded olivetol dimethyl ether and an undistillable residue which, probably, was a polymer of the initially formed menthadiene. Further study of this reaction may make possible the isolation of a monomer in which the position of the ring double bonds may be determined.

Attempts to crystallize any of the tetrahydrocannabinols have not succeeded. No reagents were discovered which gave solid derivatives from the form $\alpha_D$ −265° that could be purified. Among these may be mentioned the *p*-phenylazobenzoate, acetate, *p*-nitrobenzoate, *p*-aminobenzoate, 3,5-dinitrobenzoate, 3,5-dinitrophenylurethan, diphenyl carbamate, picrate, succinate half ester, allophanate, methyl ether, acetic acid ether and 2,4-dinitrophenyl ether. In addition condensation products with diazotized *p*-nitraniline, naphthionic acid, β-naphthylamine and 2,4,6-trinitraniline were intractable substances, as were the nitration and nitrosation products. The same was true of the products obtained by treatment

(5) Adams, Wolff, Cain and Clark, THIS JOURNAL, **62**, 2215 (1940).

(6) Adams, Hunt and Clark, *ibid.*, **62**, 735 (1940).

with mercuric acetate, bromine in acetic acid, thiocyanogen and phenylazide, one or more of which it was hoped would add to the double bond with formation of crystalline derivatives.

Ozonization of cannabidiol dimethyl ether obviously attacked not merely the double bonds but also the aromatic ring and actually in one experiment, when excess of ozone was used, caproic acid was isolated.

The ultraviolet absorption spectra of the tetrahydrocannabinols of various rotations showed no significant differences from each other or, peculiarly enough, from the spectrum of cannabidiol (see figure). They differ markedly from the absorption spectrum of the tetrahydrocannabinol with the double bond conjugated to the benzene ring, and thus it is established that the double bonds in the tetrahydrocannabinols obtained by isomerization of cannabidiol do not have the double bond conjugated to the aromatic nucleus.[7]

The tetrahydrocannabinol $\alpha_D$ −130° is physiologically active and not much less potent in its marihuana effect on dogs than higher-rotating forms. It has now been definitely established by clinical experiments that these substances (the form $\alpha_D$ −265° was actually used) have the same activity in humans as red oil or a crude hemp extract. The method of pharmacological testing by Dr. S. Loewe involving "Bioassay by Approximation" evaluating motor incoördination of dogs may, therefore, be considered a satisfactory criterion for determining whether a substance will have marihuana-like activity in humans.

## Experimental

**Isomerization of Cannabidiol with *p*-Toluenesulfonic Acid.**—A solution of 0.19 g. of *p*-toluenesulfonic acid monohydrate and 3.14 g. of crystalline cannabidiol in 100 cc. of dry benzene was refluxed for one and one-half hours. At the end of that time the alkaline Beam test was negative. The benzene solution was extracted twice with 5% aqueous bicarbonate solution and twice with water. The benzene was evaporated and the residue distilled under reduced pressure. Four fractions were collected, b. p. 169–172° (0.03 mm.), having essentially the same rotation, $[\alpha]^{29}D$ −264 to −270°, and weighing 2.32 g. *Rotation.* 0.0694 g. made up to 5 cc. with 95% ethanol at 29° gave $\alpha_D$ −3.70°; *l*, 1; $[\alpha]^{29}D$ −267°.

**Isomerization of Cannabidiol with Sulfuric Acid.**—To a solution of 1.94 g. of crystalline cannabidiol in 35 cc. of cyclohexane (free from unsaturated material) was added one drop of 100% sulfuric acid. The mixture was refluxed for one hour, at the end of which time the alkaline Beam test was negative. The solution was decanted from the sulfuric acid, washed twice with aqueous 5% bicarbonate solution and twice with water, and evaporated. The residue was distilled under reduced pressure. Three fractions were collected, b. p. 165–170° (0.1 mm.), $[\alpha]^{29}D$ −259 to −269°, weight 1.51 g. *Rotation.* 0.0381 g. made up to 5 cc. with acetone at 29° gave $\alpha_D$ −2.10°; *l*, 1; $[\alpha]^{29}D$ −264°.

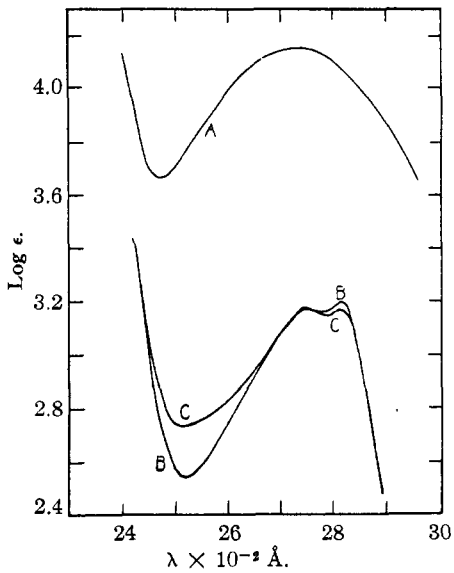



Fig. 1.—A, Synthetic tetrahydrocannabinol in ether. Ghosh, Todd and Wilkinson, *J. Chem. Soc.*, 1121 (1940), report log ε = 4.046 at 2755 Å. in ethanol. B, Tetrahydrocannabinol prepared by isomerization of cannabidiol. The spectra of the low- and high-rotating forms were so nearly identical that they are shown here as one curve. C, Cannabidiol.

Other relatively strong organic acids were ineffective in catalyzing the isomerization of cannabidiol in boiling benzene. One-tenth mole of acid per mole of cannabidiol was used in each case. The acids and lengths of time of refluxing were as follows: trichloroacetic twenty hours, 87% formic eleven hours, anhydrous oxalic fourteen hours, picric twenty-three hours, 3,5-dinitrobenzoic twenty-five hours, maleic twelve hours. At the end of each treatment the alkaline Beam test was positive. Finally, treatment with *p*-toluenesulfonic acid converted the cannabidiol to tetrahydrocannabinol of rotation $[\alpha]^{28}D$ −266 to −270°.

**Preparation of Tetrahydrocannabinol, $\alpha_D$ −130 ± 5°.**—A solution of 3.14 g. (0.01 mole) of cannabidiol in 100 cc. of absolute ethanol containing 0.0005 mole of hydrogen chloride (added as 0.5 *M* ethanolic hydrochloric acid) was refluxed on the steam-bath for eleven hours. At the end of this time the alkaline Beam test had become negative. The reaction mixture was poured into cold water and the product extracted with ether. The ether extract was washed with dilute aqueous sodium bicarbonate solution followed by water. The residue remaining upon drying and evaporating the ether was distilled; colorless, highly viscous liquid, b. p. 157–160° (0.05 mm.), $n^{20}D$ 1.5425. Five fractions of the distillate were collected, the specific rotation values of each being essentially the same. *Rotation.* 0.0645 g. made up to 5 cc. with 95% ethanol at 26° gave $\alpha_D$ −3.37°; *l*, 2; $[\alpha]^{26}D$ −130°.

(7) Adams and Baker, THIS JOURNAL, **62**, 2405 (1940).

**Isomerization of Low-Rotating to High-Rotating Tetrahydrocannabinol.**—A solution of 0.054 g. of *p*-toluenesulfonic acid monohydrate in 25 cc. of benzene was warmed on the steam-bath until the acid dissolved. To this warm solution was added 0.92 g. of tetrahydrocannabinol $[\alpha]^{26}D$ −130° and the mixture refluxed for two and one-half hours. The benzene solution was washed with water, dilute aqueous sodium bicarbonate and again with water. The residue remaining upon evaporation of the benzene was distilled onto a cold finger condenser. Three fractions were taken, the specific rotation values being $[\alpha]^{24}D$ −183, −201 and −223°. *Rotation.* (Fraction 3) 0.0692 g. made up to 5 cc. with 95% ethanol at 24° gave $\alpha D$ −3.09°; *l*, 1; $[\alpha]^{24}D$ −223°.

**Addition of Hydrogen Chloride to Tetrahydrocannabinol, $\alpha D$ −130°.**—A solution of 1.0 g. of tetrahydrocannabinol $[\alpha]^{27}D$ −130° in 75 cc. of dry ether was cooled to 0° and saturated with dry hydrogen chloride. A calcium chloride drying tube was placed in the mouth of the flask and the flask and contents were allowed to stand at 0° overnight. The ether and hydrogen chloride were evaporated at room temperature by a stream of dry air. The residue was dissolved in 100 cc. of ether and the resulting solution washed several times with dilute aqueous sodium bicarbonate followed by water. The ether solution was dried with Drierite and the ether evaporated by a stream of dry air. To remove the last traces of ether the residue was warmed to 80° while the pressure was reduced to 17 mm. The residue was a clear red resin which gave a strong test for chloride ion when an ethanolic solution was tested with ethanolic silver nitrate solution. *Rotation.* 0.0250 g. made up to 5 cc. with 95% ethanol at 26° gave $\alpha D$ −0.82°; *l*, 2; $[\alpha]^{26}D$ −82°.

The material was distilled with bath temperature at 185° and 0.05 mm. pressure. A trap containing solid potassium hydroxide was placed between the flask and the pump. After the distillation was complete the potassium hydroxide was dissolved in water, acidified with nitric acid and tested for chloride ion. A heavy precipitate of silver chloride indicated that hydrogen chloride had been evolved during the distillation. Three fractions of distillate were collected, having specific rotations of −196, −197 and −203°, respectively. *Rotation.* (Fraction 3) 0.0333 g. made up to 5 cc. with 95% ethanol at 26° gave $\alpha D$ −2.70°; *l*, 1; $[\alpha]^{26}D$ −203°.

**Hexahydrocannabinol from Tetrahydrocannabinol, $\alpha D$ −130°.**—A solution of 1.411 g. of tetrahydrocannabinol, $[\alpha]^{26}D$ −133°, in glacial acetic acid was reduced with hydrogen and platinum oxide as previously described.[3] Four fractions of distillate were collected having essentially the same specific rotation which checked with that reported for hexahydrocannabinol prepared by reduction of higher-rotating tetrahydrocannabinols. *Rotation.* (Fraction 3) 0.0312 g. made up to 5 cc. with 95% ethanol at 26° gave $\alpha D$ −0.91°; *l*, 2; $[\alpha]^{26}D$ −73°.

**Attempted Shift of the Double Bond in Dihydrocannabidiol Dimethyl Ether.**—To a solution of 0.07 g. of *p*-toluenesulfonic acid monohydrate in 35 cc. of dry benzene was added 1.28 g. of dihydrocannabidiol dimethyl ether ($n^{20}D$ 1.5185) and the mixture refluxed for four hours. The benzene solution was washed with water, dilute aqueous sodium bicarbonate and again with water. After evaporation of the benzene the residue was distilled, b. p. 100–103° (0.05 mm.). A light brown resin remaining in the flask would not distil even though the bath temperature was raised to 225°. By the lack of optical activity, index of refraction ($n^{20}D$ 1.5062) and the analysis, the distillate was shown to be olivetol dimethyl ether.

*Anal.* Calcd. for $C_{13}H_{20}O_2$: C, 74.93; H, 9.68. Found: C, 75.47; H, 9.75.

**Ozonization of Cannabidiol Dimethyl Ether and Isolation of a Derivative of Formaldehyde.**—A solution of 0.04 g. of cannabidiol dimethyl ether in 5 cc. of glacial acetic acid was ozonized for ten minutes with 2.5% ozone. It was then poured into warm water and allowed to stand for thirty minutes. The solution was neutralized with dilute aqueous sodium hydroxide and 0.1 g. of methone in 2 cc. of ethanol was added. When the solution was cooled there was obtained 0.022 g. of crystalline product; m. p. 189–191°. This corresponded to a 67% yield for 1 mole of formaldehyde. A sample of the derivative was prepared from formalin; m. p. 190–191°; mixed melting point of the two was 190–191°.

**Ozonization of Cannabidiol Dimethyl Ether Followed by Cleavage with Chromic Acid.**—A solution of 1.75 g. of cannabidiol dimethyl ether in 30 cc. of glacial acetic acid was ozonized at room temperature for eighty-four minutes. Two and one-half per cent. ozone, at the rate of 0.000183 mole per minute, was used. This was about 150% of the theoretical amount for two double bonds. A solution of 0.8 g. of chromic oxide (80% of theoretical for 3 atoms of oxygen) in acetic acid was dropped slowly into the ozonide solution with stirring. About 25 cc. of water was added and the mixture warmed at 50–60° for thirty minutes. It was then poured into an excess of water and the oily product extracted with a little benzene. Two extractions with aqueous 5% sodium bicarbonate solution followed by acidification gave only a small amount of acidic product. The semicarbazone, 2,4-dinitrophenylhydrazone, and *p*-bromophenacyl ester derivatives were made but none was a solid. The neutral benzene solution that had been extracted was evaporated, taken up in 20 cc. of acetic acid, and again oxidized by 0.8 g. of chromic oxide in 20 cc. of water. After the solution had been warmed on the steam cone overnight most of the solvent was evaporated and excess water was added. When the oily product was taken up in benzene and extracted with 5% aqueous sodium hydroxide, about 0.15 g. of an acidic oil was obtained but attempts to form solid derivatives failed.

The neutral benzene solution from the above extraction was evaporated and derivatives were made on the residual oil. A 2,4-dinitrophenylhydrazone, sparingly soluble in alcohol, was obtained. It crystallized well from a mixture of acetone and alcohol in orange needles, m. p. 228–230°.

*Anal.* Calcd. for $C_{20}H_{24}O_6N_4$: C, 57.68; H, 5.94; N, 13.45. Found: C, 57.84, 57.76, 57.90; H, 5.60, 6.22, 5.86; N, 13.21, 13.36.

**Reaction of Cannabidiol with 8% Ozone—Isolation of *n*-Caproic Acid.**—In this experiment 8% ozone flowing at the rate of 0.0008 mole per minute was used in large excess. A solution of 4 g. of cannabidiol in 100 cc. of glacial acetic acid was ozonized for eight hours. An equal volume of water was added and the solution was refluxed overnight. The solution was cooled and potassium permanganate

added until the excess permanganate color remained for a few minutes, with the object of destroying oxalic acid and oxidizing any aldehydes to acids. Excess permanganate was destroyed by the addition of a little sodium bisulfite and the manganese dioxide was removed by filtration. The solution was then steam distilled. From the residual solution only an intractable tar was obtained. The steam distillate was neutralized with sodium hydroxide and evaporated to dryness. The salt was then acidified and the solution extracted with ether and distilled. After the acetic acid had been removed a small amount of oily acid remained. It was converted into a crystalline *p*-bromophenacyl ester, m. p. 63°.

A mixed melting point with the *p*-bromophenacyl ester of *n*-caproic acid showed no depression.

This compound was obtained by the same procedure when cannabidiol dimethyl ether was treated with 150% of the theoretical amount of 8% ozone. The residue from steam distillation was again an intractable tar. Apparently this concentration of ozone was attacking the aromatic ring.

## Summary

1. New procedures for isomerizing cannabidiol have resulted in synthesizing two tetrahydrocannabinols, $\alpha_D$ −130° and $\alpha_D$ −265°, of essentially constant rotation. Previously obtained tetrahydrocannabinols are assumed to be mixtures.

2. Additional evidence for shifting of the double bond in conversion of the low-rotating to a higher-rotating tetrahydrocannabinol is presented. The low-rotating form adds hydrogen chloride and loses it on distillation to give a higher-rotating form.

3. The form $\alpha_D$ −130° reduces to a hexahydrocannabinol of identical rotation with that obtained by reduction of higher-rotating forms.

4. The form $\alpha_D$ −130° has about the same marihuana activity as the higher-rotating forms. Clinical tests have demonstrated the tetrahydrocannabinols (the form used was $\alpha_D$ −265°) to have exactly the same physiological activity in humans as crude hemp extract.

5. Dihydrocannabidiol dimethyl ether, when heated with *p*-toluenesulfonic acid in benzene, cleaves to olivetol dimethyl ether and an undistillable compound, presumably a polymer of menthadiene.

URBANA, ILLINOIS RECEIVED JUNE 5, 1941

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

# The Condensation of α-Picoline and Quinaldine with Active Ketones

BY S. M. MCELVAIN AND HAROLD G. JOHNSON

While a methyl group in the α-position of the pyridine or quinoline nucleus possesses quite a high reactivity when compared with one in any of the other positions of these nuclei, it is relatively unreactive in comparison with a methyl (or methylene) group adjacent to the carbonyl group of a ketone, aldehyde or an ester. A few representative examples of this low reactivity may be cited: paraformaldehyde and α-picoline at 140° for nine hours give a 32% yield of β-2-pyridylethyl alcohol[1]; only a 4–6% yield of 2-pyridylisopropyl alcohol may be obtained from the reaction of α-picoline with acetaldehyde[2]; in order to obtain α-stilbazole in as much as 9% yields it is necessary to heat a mixture of α-picoline, benzaldehyde and freshly fused zinc chloride at 200° for twelve to fourteen hours.[3] If, however, the more active carbonyl compound, chloral, is allowed to react with α-picoline it has been found possible to obtain the resulting condensation product, 1,1,1-trichloro-2-hydroxy-3-(2-pyridyl)-propane in yields as high as 70% of the theoretical.[1] In these representative examples it is the carbonyl group of an aldehyde that reacts. Ketones, in general, do not condense with the methyl group of α-picoline except in a few cases in which sodamide has been used as the condensing agent.[4]

Several years ago, in this Laboratory, Walter,[5] in the course of some other work, found that oxomalonic ester in an excess of boiling α-picoline readily condensed with the picoline to give a quite satisfactory yield of ethyl α-picolyltartronate (III). Along with this product there was obtained a small amount of a yellow substance, the structure (IV) of which is discussed below. This greater reactivity of α-picoline with a carbonyl group that is activated by adjacent negative

(1) Tullock and McElvain, THIS JOURNAL, **61**, 961 (1939).

(2) Ladenburg, *Ann.*, **301**, 140 (1898); Meisenheimer and Mahler, *ibid.*, **462**, 301 (1928).

(3) Bailey and McElvain, THIS JOURNAL, **52**, 1636 (1930).

(4) Chichibabin, *Bull. soc. chim.*, **3**, 1607 (1936).

(5) Unpublished work of Lewis A. Walter.