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

THE CONFIGURATION OF METHYLISOPROPYLCARBINOL WITH A NOTE ON RACEMIZATION

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The only carbinols whose configurations have been directly correlated are those having straight chains or those with the branched chain at least one carbon atom removed from the asymmetric carbon atom. The first attempt to correlate carbinols with the branched chain directly attached to the asymmetric carbon atom was made by Levene and Marker,[1] who deduced the configuration of the isopropylcarbinols from their abnormal rotatory powers. They concluded that these carbinols had opposite configurations from those of the corresponding straight chain carbinols; in support of this conclusion, they found that levo methylethylisopropylmethane was configurationally related to dextro methylethylpropylmethane.[2]

However, the first member of the isopropyl series, methylisopropylcarbinol, has a comparatively low rotation. For this reason it is not possible to deduce its configuration with the same degree of certainty that Levene and Marker attained in the case of the higher members of the series. This paper therefore deals with the direct correlation of methylisopropyl- and methylpropylcarbinols. It now seems certain that the two carbinols are configurationally related when both have the same sign of rotation, contrary to the conclusion of Levene and Marker.

The correlation of levo methylisopropyl- and levo methylpropylcarbinol was accomplished by synthesis from dextro ethyl lactate. Fortunately commercial ethyl lactate had a sufficient activity to render a resolution of lactic acid unnecessary.[3] By ethylating this ester, the rotations were increased to such an extent that there could be no doubt that the rotations were real. In no reaction was the asymmetric carbon atom involved. The general scheme of correlation is as indicated.

The dehydration of the ethoxycarbinol I to give the optically active unsaturated ether II was the key to the correlation. Tschugaeff's xanthogenate method of dehydration avoids rearrangements, as is shown so well by the formation of bornylene from borneol,[4] and tertiary-butylethylene from methyl-tertiary-butylcarbinol.[5] The hydrogenation of II caused an inversion of the sign of rotation just as with unsaturated carbinols.[6] Fi-

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[1] Levene and Marker, *J. Biol. Chem.*, **90**, 669 (1931).

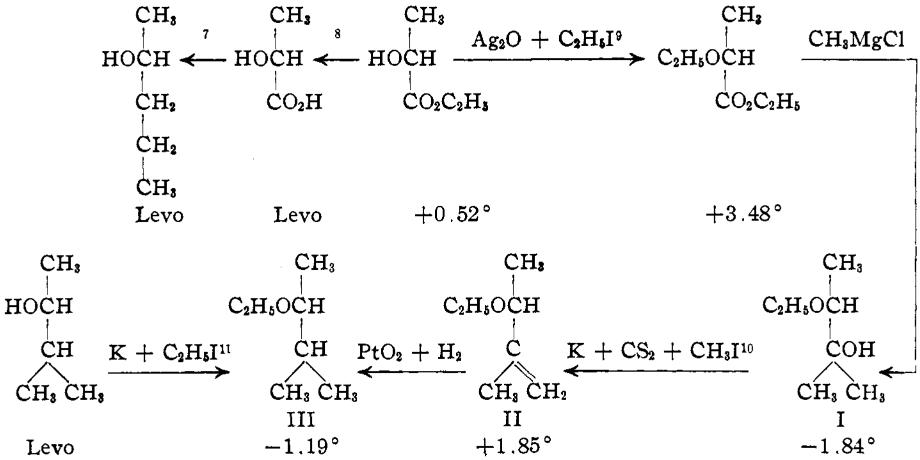
[2] Levene and Marker, *ibid.*, **91**, 405 (1931).

[3] Compare McKenzie, *J. Chem. Soc.*, **87**, 1373 (1905).

[4] Tschugaeff, *Chem. Centr.*, I, 94 (1905).

[5] Fomin and Sochanski, *Ber.*, **46**, 246 (1913).

[6] Levene and Haller, *J. Biol. Chem.*, **83**, 579 (1929).



nally, the saturated ether III thus obtained was compared with the dextro ethyl ether of methylisopropylcarbinol prepared from the dextro carbinol, and the two were found to be chemically identical.

It is interesting to note that there was no racemization of the ethoxy tertiary carbinol I when heated for ten hours at 190° with metallic potassium, while methylisopropylcarbinol under about the same conditions (180°) was almost completely racemized in four hours. These facts fit in well with the mechanism of racemization and rearrangement of alcoholates proposed recently by Hückel,[12] which involves the loss of hydrogen with the formation of an unsaturated (hence inactive) intermediate, followed by reduction to the rearranged (racemized) substance.

The ethoxy tertiary alcoholate from I has no hydrogen on the carbon atom to which the alcoholate group is attached, and hence cannot lose hydrogen. This case is then similar to the case of those acids which do not racemize because there is no enolizable hydrogen in the α-position. On the other hand, methylisopropylcarbinol alcoholate possesses such a hydrogen and does racemize.

The correlation of levo methylisopropyl- and levo methylpropylcarbinol shows that a change of a propyl to an isopropyl group lowers the optical rotation without reversing the sign. The effect of the branched chain when directly attached to the asymmetric carbon atom is therefore to depress the rotatory power. The other members of the isopropyl series, *viz.*, ethyl-, propyl-, and butyl-isopropylcarbinols have higher rotations than the

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[7] Levene and Haller, *J. Biol. Chem.*, **72**, 591 (1927).

[8] Karrer, Escher and Widmer, *Helv. Chim. Acta*, **9**, 303, 323 (1926).

[9] Purdie and Irvine, *J. Chem. Soc.*, **75**, 483 (1899).

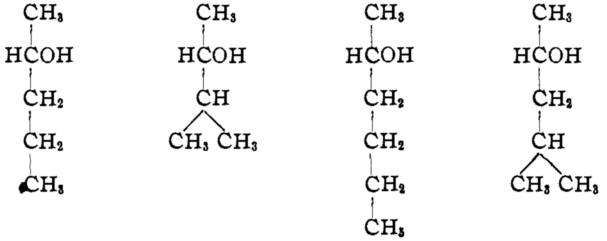
[10] Tschugaeff, *Ber.*, **32**, 3332 (1889); Gandurin, *ibid.*, **41**, 4362 (1908).

[11] The material actually used was dextrorotatory.

[12] Hückel, *Ber.*, **64B**, 2137 (1931).

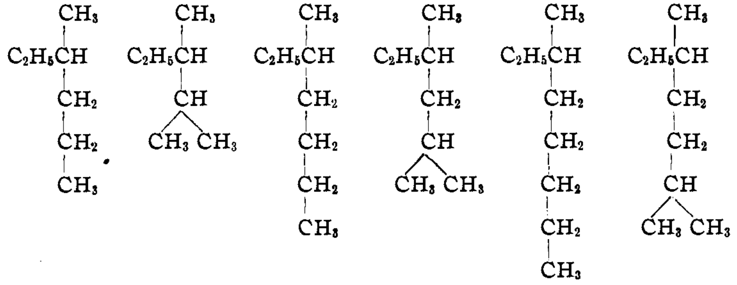
corresponding straight chain carbinols; but as Levene and Marker[1] suggested, they are undoubtedly oppositely configurated, and show the depressing effect of the isopropyl group by a change in the sign of rotation. Therefore, according to the rule of Levene and Haller,[13] the isopropyl radical, while heavier than the methyl, acts as if lighter than the ethyl group.

When, however, the branched chain is once removed from the asymmetric carbon atom, then the rotation is exalted, as Levene and Walti[14] have already shown.



[M]D +12.1°[15] +4.3° +11.8° +20.9°

Levene and Marker[16] found a similar depression and exaltation in the hydrocarbon series, except that the depression caused by the isopropyl group when next to the asymmetric carbon atom was sufficient to invert the sign of rotation. On the other hand, however, they found that when twice removed from the asymmetric carbon atom, the effect of the branched chain was negligible.



[M]D +9.9° −15.7° +11.4° +21.3° +12.0° +11.9°

It may seem strange that the effect of a group should be so different when attached to, and once removed from, the asymmetric carbon atom. A difference in polarities, as suggested by acid dissociation constants at least, does not seem to be the cause, for butyric and isobutyric acids have about the same dissociation constants, while the propyl- and isopropyl-

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[13] Levene and Haller, *J. Biol. Chem.*, **79**, 475 (1928).

[14] Levene and Walti, *ibid.*, **94**; 367 (1931).

[15] Maxima by Pickard and Kenyon, *J. Chem. Soc.*, **99**, 45 (1911).

[16] Levene and Marker, *J. Biol. Chem.*, **95**, 1 (1932).

carbinols have very different rotations. Most probably the real cause is a difference in the absorption bands in the ultraviolet, as Kuhn and Freudenberg[17] have already indicated.

There is also a possibility that asymmetry plays an important role. From dissociation constants and absorption spectra, one can reason that the phenyl group should have the opposite effect from the isopropyl and tertiary-butyl groups. The correlation of carbinols containing these groups directly attached to the asymmetric carbon atom should be, therefore, of theoretical value. Work in this direction is now in progress.

I am indebted to Dean Frank C. Whitmore for making available the facilities of this Laboratory; and to the Mallinckrodt Chemical Works which so generously supplied the large quantities of iodine necessary in this work. Part of the funds required for this research were privately contributed.

Experimental Part

In this work all rotations are for the homogeneous state.

Dextro Ethyl Lactate, $CH_3CHOHCO_2C_2H_5$.—Eastman's commercial ethyl lactate $[\alpha]_D$ +0.45°, was fractionated through a 91-cm. adiabatic controlled reflux column (column A); b. p. 151.6–152.2°; $[\alpha]^{27}_D$ +0.52°. Another sample was less active: $[\alpha]^{27}_D$ +0.30°; n^{20}_D 1.4127.

Dextro Ethyl *α*-Ethoxy Propionate, $CH_3CHOC_2H_5COOC_2H_5$.[6]—To 196 g. of ethyl lactate $[\alpha]^{27}_D$ +0.30°, dissolved in 936 g. (3.6 equiv.) of ethyl iodide, was added gradually with mechanical stirring 696 g. (1.8 equiv.) of dry silver oxide. The reaction started on warming. After all the oxide had been added, the mixture was boiled for several hours and then allowed to stand overnight. The next morning, 460 g. of ethyl iodide was added, and the boiling continued all day. After standing warm overnight, dry ether was added, the silver compounds filtered off, and the resulting solution fractionated directly through column A.

1st fraction: b. p. (731 mm.) 152.0–153.6°; 66.5 g., $[\alpha]^{23}_D$ +1.56°, n^{20}_D1.4021
2d fraction: b. p. (731 mm.) 153.6–154.3°; 104.5 g., $[\alpha]^{23}_D$ +1.62°, n^{20}_D1.4015
(Thermometer completely immersed in the vapor)

Forty cc. of the second fraction was shaken thoroughly with water, with 2% aqueous sodium carbonate, dried over anhydrous potassium carbonate and refractionated through a similar 61 cm. column (column B):[18] b. p. (730 mm.) 152.7–152.8°; $[\alpha]^{23.5}_D$ +1.69°; n^{20}_D 1.4011.

The ethoxy ester prepared from the more active lactate of $[\alpha]^{27}_D$ +0.52° had the activity $[\alpha]^{24}_D$ +3.48°.

Levo 2-Ethoxy-3-methylbutanol-3, $CH_3CHOC_2H_5COH(CH_3)_2$.—109 g. of the ethoxy ester, $[\alpha]^{24}_D$ +3.48°, was added to 4–5 equivalents of methylmagnesium chloride in the usual way. After standing at room temperature for two days with intermittent stirring, the reaction mixture was decomposed with ice and ammonium chloride, and the product extracted with ether. The ether was then washed with 10% aqueous potassium

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[17] W. Kuhn, *Ber.*, **63,** 199 (1930); W. Kuhn, Freudenberg and Wolf, *ibid.*, **63,** 2368 (1930).

[18] Karvonen reported: b. p. (750 mm.) 153–155°; n^{20}_D 1.40125. *Ann. Acad. Sci. Fennicae,* [6] **10A,** 1 (1916).

hydroxide, dried over sodium sulfate and fractionated through column A. The main fraction, b. p. 140.2–141.7°, weighed 84 g., yield 85%. This material was redistilled in a modified Claisen flask from 8 g. of sodium metal:[19] b. p. 140.0–140.5°; $[\alpha]_D^{29.5}$ −1.84°; n_D^{20} 1.4111.

Anal. (micro). Calcd. for $C_7H_{16}O_2$: C, 63.6; H, 12.1; OC_2H_5, 34.1. Found: C, 63.0; H, 11.8; OC_2H_5, 35.5.

Another sample from the less active ethoxy ester, $[\alpha]_D^{23.5}$ +1.69°, was fractionated through column B: b. p. (728 mm.) 140.1–140.4°; $[\alpha]_D^{27}$ −0.83°. In order to remove any unchanged ester the material was boiled for eight hours with alcoholic potassium hydroxide, steam distilled, refractionated and distilled from sodium metal: b. p. (736 mm.) 140.5–140.8° (bath 200°); $[\alpha]_D^{30.5}$ −0.83°.

Anal. (micro). Calcd. for $C_7H_{16}O_2$: C, 63.6; H, 12.1; OC_2H_5, 34.1. Found: C, 63.1; H, 12.0; OC_2H_5, 37.4. Further attempts to correct the ethoxyl value reduced it to only 36.4%.

Dextro 2-Ethoxy-3-methylbutene-3, $CH_3CHOC_2H_5CCH_3{=}CH_2$.—40.6 g. of the ethoxycarbinol, $[\alpha]_D^{29}$ −1.84°, dissolved in 600 cc. of *p*-cymene[20] was boiled with 20 g. (2 equiv.) of clean, bright potassium metal until no more metal was consumed (±three hours); 50 cc. of the solvent was now distilled off to remove any unreacted carbinol. The almost colorless mixture was cooled, most of the potassium removed mechanically, and 575 cc. of dry ether added. Now 46.8 g. (2 equiv.) of carbon disulfide was added, precipitating the yellow xanthogenate. After one hour at room temperature, 110 g. (2.5 equiv.) of methyl iodide was added, and the mixture put in the hood overnight. The next morning, after boiling gently for five hours, as much as possible of the reaction mixture was distilled off on the steam-bath. Only a small amount of mercaptan had formed up to this point.[21] The distillation was continued, using a free flame. Soon a vigorous fuming occurred as the xanthogenate decomposed. The distillation was continued until the temperature rose to the boiling point of the pure solvent. The distillate was extracted with 5% aqueous potassium hydroxide, and then with a saturated solution of mercuric chloride, until no more mercaptide formed. After washing well with water and drying over sodium sulfate, the ether was fractionated off. During this process, a considerable amount of a white substance precipitated. The ether solution was therefore decanted, washed thoroughly with aqueous sodium carbonate and potassium hydroxide to remove any mercuric compounds, dried over anhydrous potassium carbonate and fractionated through column B

$$\left.\begin{array}{l}\text{1st fraction, b. p. 90–94°; } [\alpha]_D^{27}\ +1.02°;\ \text{4 g.}\\ \text{2d fraction, b. p. 94–99°; 21 g.}\end{array}\right\}\text{71\% yield}$$

The second fraction was refractionated

1st fraction, b. p. (730 mm.), 94.0–97.1°; $[\alpha]_D^{27.5}$ +1.65°
2d fraction. b. p. (730 mm.), 97.1–98.1°; $[\alpha]_D^{25.5}$ +1.85°

Part of this second fraction, b. p. 98.0°, n_D^{20} 1.4039, was dried over calcium chloride.

Anal. (micro). Calcd. for $C_7H_{14}O$: C, 73.6; H, 12.4. Found: C, 73.5; H, 12.2.

Ethoxyl values were too high, due to contamination of diethyl ether.

The new substance was actively unsaturated. It absorbed bromine in cold carbon tetrachloride solution instantly. Likewise, it reduced cold aqueous permanganate in-

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[19] Compare Ciamician and Silber, *Ber.*, **44,** 1554 (1911).

[20] The cymene, b. p. 175.0–175.5°, was purified by boiling with potassium metal for five hours.

[21] Gandurin[7] reported tertiary xanthogenates as decomposing at room temperature

stantly. The reduction of permanganate in acetone solution was slow. The compound possessed a clean, strong, peppermint-like odor, there being no trace of any methyl mercaptan.

Levo 2-Ethoxy-3-methylbutane, $CH_3CHOC_2H_5CH(CH_3)_2$.—12.5 g. of the unsaturated ether, $[\alpha]^{25.6}_{D}$ +1.85°, was reduced in glacial acetic acid with Adams' platinum catalyst and hydrogen at 3 atmospheres pressure. There was a fairly long induction period before the reduction started. Approximately the correct amount of hydrogen was absorbed. The solution was then decanted into a liter separatory funnel, ice added and the mixture neutralized with 20% aqueous potassium hydroxide. When strongly alkaline, the solution was extracted with ether, which was washed with aqueous potassium hydroxide, and water, then dried over calcium chloride and fractionated through column B. The main fraction, b. p. (732 mm.) 99.2–100.0°, weighed 6.5 g. This material showed no unsaturation, giving no reactions with either bromine or permanganate. It had a pleasant camphor-like odor, identical with that of the ethyl ether of methylisopropylcarbinol prepared from the carbinol. The saturated ether was levorotatory, $[\alpha]^{27.5}_{D}$ −1.21°. The ether was boiled in a small Claisen flask over potassium metal, and then distilled: b. p. 99.0–99.2°, $[\alpha]^{25}_{D}$ −1.19°, n^{20}_{D} 1.3873.

Anal. (micro). Calcd. for $C_7H_{16}O$: C, 72.4; H, 13.9. Found: C, 72.5: H, 13.9.

As the substance gave high analyses for ethoxyl, due to contamination of diethyl ether, it was refractionated through column B. The fraction, b. p. 100.0°, was now pure, n^{20}_{D} 1.3877.

Anal. (micro). Calcd. for $C_7H_{16}O$: C, 72.4; H, 13.9: OC_2H_5, 38.8. Found: C, 72.3: H, 14.0: OC_2H_5, 38.4.

Dextro Methylisopropylcarbinol, $CH_3CHOHCH(CH_3)_2$.—The carbinol, b. p. 110.0–110.1°, prepared from isobutyric aldehyde and methylmagnesium chloride, was converted into the acid phthalate with phthalic anhydride and pyridine, and then resolved with brucine in acetone solution.[22] Four recrystallizations of the salt were sufficient. The carbinol was recovered in the usual way and fractionated through column B: b. p. (734 mm.) 111.6–111.8°, $[\alpha]^{24}_{D}$ +0.90°, n^{20}_{D} 1.4090.

Dextro 2-Ethoxy-3-methylbutane, $CH_3CHOC_2H_5CH(CH_3)_2$.—29.3 g. of the carbinol, $[\alpha]^{24}_{D}$ +0.90°, dissolved in 475 cc. of *p*-cymene was boiled with 16 g. of clean potassium metal. After four hours, as no more potassium seemed to react, the mixture was cooled, and 70 g. of ethyl iodide was added. On warming the iodide reacted, precipitating potassium iodide. The reaction products were now boiled until most of the metal had disappeared, and then allowed to stand overnight. The following morning the products were distilled out directly. The material, b. p. 90–175°, was fractionated through column B. The fraction of b. p. 99.0–99.8° was the desired ether. It was purified by boiling for one hour over metallic potassium, distilling and boiling again over fresh potassium. The final distillate, from a small Claisen flask, b. p. 99.0–99.4°, was dextrorotatory; $[\alpha]^{25}_{D}$ +0.60°, n^{20}_{D} 1.3876.

Anal. (micro). Calcd. for $C_7H_{16}O$: C, 72.4; H, 13.9; OC_2H_5, 38.8. Found: C, 72.3; H, 14.1; OC_2H_5, 38.4.

Considerable amounts of unreacted carbinol were recovered. These were refractionated through column B, b. p. 111.0–111.3°, n^{20}_{D} 1.4097. No optical activity could be detected in a one decimeter tube.

Action of Heat (190°) on the Alcoholate of Levo 2-Ethoxy-3-methylbutanol-3.—Fifteen grams of the carbinol, $[\alpha]^{31}_{D}$ −0.85°, n^{20}_{D} 1.4098, dissolved in 340 cc. of decaline (b. p. 188–190°), was treated with 10 g. (2.3 equiv.) of clean potassium metal which was then converted to powder by warming and shaking. After warming to 100–120° for

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[22] Pickard and Kenyon, *J. Chem. Soc.*, **99**, 45 (1911).

a few hours, shaking frequently, the mixture was allowed to stand overnight, all of the alcoholate remaining in solution. The next day, the solution was boiled for ten hours. The clear solution gradually became black, due to the formation of tarry matter. At the end of the ten hours, all the metal had disappeared. Now after cooling, 35 cc. of methyl alcohol was added, the mixture shaken well, and distilled directly. The material b. p. 65–185° was fractionated through column B twice. About 2 g. of the original carbinol was thus obtained, b. p. 138–143°, n^{20}_{D} 1.4118. The optical activity was unchanged, $[\alpha]^{28}_{D}$ $-0.82°$. There had been, therefore, decomposition apparently but no racemization.

Summary

1. Levo methylisopropyl- and levo methylpropylcarbinols are configurationally related.

2. A tertiary alcoholate was not racemized by heating at 190° for ten hours; this supports Hückel's mechanism of racemization and rearrangement of alcoholates.

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[Contribution from the Chemical Laboratory of the University of Toronto]

THE FRIEDEL AND CRAFTS REACTION. SOME UNSYMMETRICAL ACID ANHYDRIDES AND THEIR BEHAVIOR WITH BENZENE AND ALUMINUM CHLORIDE

By J. M. Zeavin and A. M. Fisher

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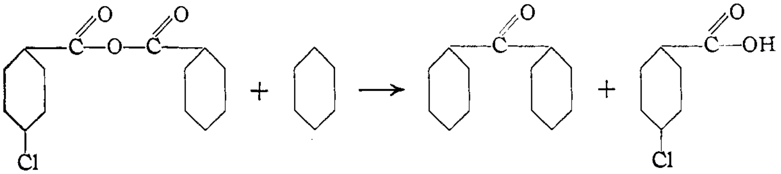
Previous research in this Laboratory on the Friedel and Crafts reaction—the production of acids and ketones from anhydrides, aromatic hydrocarbons and aluminum chloride—has been concerned with anhydrides of single acids. The purpose of the present research was to determine the course of the reaction using anhydrides which would give two acids on hydrolysis. With mono-*p*-chlorobenzoic anhydride, for example, there are three possibilities



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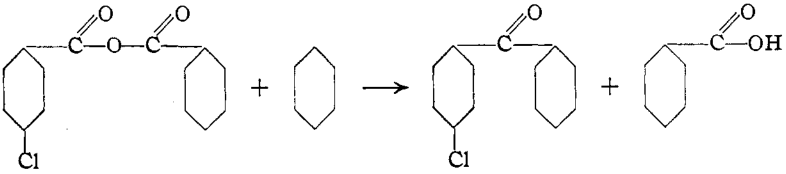

(2)

(3) The ketones might be a mixture of benzophenone and mono-*p*-chlorobenzophenone. In this paper a number of such anhydrides have