type and permit the conclusion that the tautomerization between α-*s*-butylpyridine and its isomeric enamine does not involve solvolytic ionization.

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[CONTRIBUTION FROM CHANDLER LABORATORY, COLUMBIA UNIVERSITY]

The Resolution of 2,4-Dimethylhexan-4-ol[1]

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Despite the successful resolution of many secondary alcohols[2] an unequivocal resolution of a tertiary, aliphatic alcohol of the type RR′R″COH has not been reported.[3] The resolution of α-terpineol[4] involves a tertiary alcohol in which the carbinol group is not the center of asymmetry, while the resolution of phenyldiphenyl-α-naphthylcarbinol[5] is probably complicated by a molecular asymmetry due to hindered rotation. The resolution of linalool[6] suffers not only from incompleteness but, more seriously, from the absence of an experimental demonstration that the small observed activity is due to resolved linalool rather than to a resolved impurity. In this paper the resolution of 2,4-dimethylhexan-4-ol (I, methylethylisobutylcarbinol) is described.

The choice of I for resolution attempts has been dictated by the high molecular rotations of methylisobutylcarbinol (±20.4°) and ethylisobutylcarbinol (±24.6°) in contrast to the rotations of methyl- and ethyl-, *n*-propyl, isopropyl- and *n*-butylcarbinols (±2.0 – ±15.4°), and by the desire to minimize olefin formation by avoiding juxtaposition of a tertiary hydrogen with the tertiary carbinol.

The preparation of I by the method of Clarke[7] from methyl isobutyl ketone and ethylmagnesium bromide is more satisfactory than by the converse method of the reaction of methyl ethyl ketone with isobutylmagnesium bromide. Attempts to prepare hydrogen 2,4-dimethylhexyl-4-phthalate (II) by the reaction *in situ* of the bromomagnesium salt of I with phthalic anhydride are unsuccessful.[8] However, when a benzene solution of the potassium salt of I is added to a benzene solution of phthalic anhydride according to the general method of Fuller and Kenyon,[4] II is obtained in excellent yield. While II is not crystalline and decomposes slowly on standing, its barium salt can be crystallized from ether–pentane and is indefinitely stable.

The resolution of I, pursued through the fractional crystallization of brucine 2,4-dimethylhexyl-4-phthalate (III), proceeds slowly until the head fraction changes from heavy needles to a mixture of these and tight hemispherical pellets between the fourth and sixth crystallization. By the twelfth crystallization, the hemispherical form predominates and the resolution proceeds more rapidly. Toward the end the heavy needles no longer appear in the head fraction and the optical activity becomes constant. These relations are reflected in the variation of the m. p. of III and the rotation of corresponding II shown in Fig. 1.

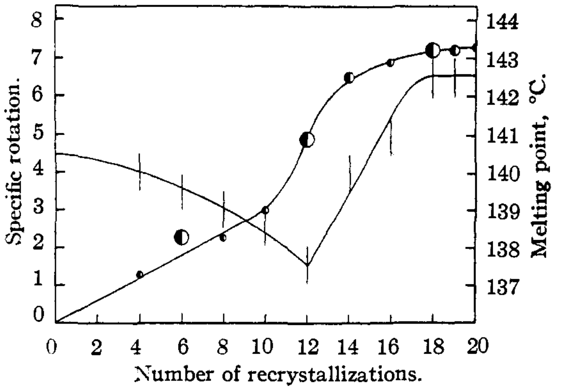

Fig. 1.—The vertical segments represent the m. p. of the head fractions in the fractional crystallization of III. The half-shaded circles represent the specific rotations of II derived from corresponding III.

Pure brucine (+)-2,4-dimethylhexyl-4-phthalate (+III), m. p. 142.5°, gives hydrogen (+)-2,4-dimethylhexyl-4-phthalate (+II), $[\alpha]^{25}\text{D}$ + 7.3°. This dextrorotatory isomer is considered to be optically pure on the grounds that no significant improvement can be made by further crystallization of the brucine salt. However, in having failed to find a base capable of effecting complete resolution of (–)-II, we have left unsatisfied the more valid criterion of optical purity.

The melting point diagram of mixtures of *r*-III (m. p. 140.5°) and (+)-III (m. p. 142.5°) shows a slight but definite minimum (m. p. 138°) which permits the conclusion that the brucine salt of *r*-II

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* Harvard University Ph.D. 1943.

[1] This publication is part of a dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Faculty of Pure Science, Columbia University. An extended version of the dissertation may be borrowed from the chemical Library on interlibrary loan. A preliminary communication has appeared in THIS JOURNAL, **70**, 3966 (1948).

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[2] Ingersoll, "Organic Reactions," John Wiley and Sons, New York, N. Y., 1944, Vol. 2, p. 376.

[3] Of several explanations for the failure, that communicated between Wilson and Kenyon, *Trans. Faraday Soc.*, **37**, 706 (1941), is of interest.

[4] Fuller and Kenyon, *J. Chem. Soc.*, **125**, 2304 (1924).

[5] Wallis, THIS JOURNAL, **54**, 1695 (1932).

[6] Paolini and Diviza, *Atti accad. Lincei*, [5] **23**, 171 (1914).

[7] Clarke, THIS JOURNAL, **30**, 1144 (1908).

[8] Compare Fessler and Shriner, *ibid.*, **58**, 1384 (1936).

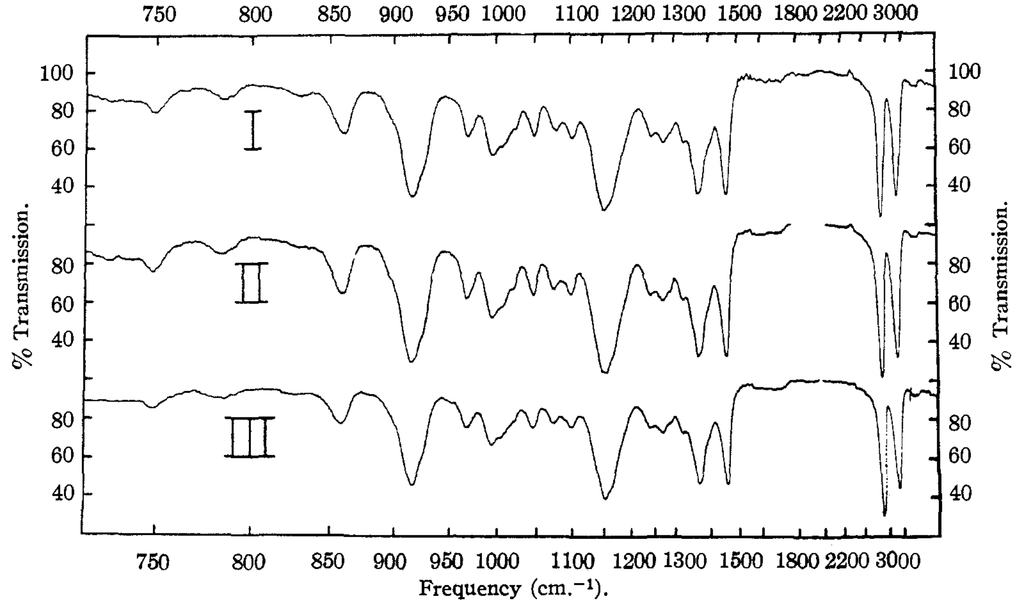

Fig. 2.—Infrared spectra of 2,4-dimethylhexan-4-ol: I, optically pure levo (−2.72°); II, racemic; III, partially resolved dextro (+1.55°).

is a 1:1 compound (partial racemate) of (+)-III and (−)-III. Inherent in this conclusion is an explanation of the apparent difficulties attending the resolution of tertiary alcohols.

Regeneration of optically active alcohol from II without racemization is theoretically best effected under conditions which permit the formation of alcohol by attack of a nucleophilic reagent at the carbonyl group alone. Ethylmagnesium bromide and, more conveniently, lithium aluminum hydride are two reagents of this type which give I in 50 and 85% of the theoretical yield, respectively. From optically pure (+)-II (+7.3°) there is obtained (−)-I (−2.72°). The absence of racemization during the regeneration is proved by a series in which (+)-I, obtained from II (−1.6°) by treatment with lithium aluminum hydride, is reconverted through the potassium salt to II of undiminished rotation (−1.6°).

The structural identity of the optically active carbinol with the racemic starting material, strongly suggested by analysis, b. p., index of refraction and density, is established beyond reasonable doubt by the superimposability of the infrared spectra in Fig. 2.[9]

With great pleasure and gratitude we acknowledge the unstinted assistance of Professor Ralph S. Halford and of Dr. Abraham Savitsky.

Experimental[10]

2,4-Dimethylhexan-4-ol (I).—An ethereal solution (1 l.) of methyl isobutyl ketone (880 ml., Carbide and Carbon Chemicals Co.) was added to ethereal (1750 ml.) ethylmagnesium bromide (204 g. of magnesium and 655 ml. of ethyl bromide). After being poured into iced 1 *N* hydrochloric acid, the ether solution was washed with water, 5% sodium carbonate, again with water, dried with anhydrous potassium carbonate and concentrated at the aspirator. Distillation gave 614 g. of I, b. p. 152–153°; $n^{18}\text{D}$ 1.4277; $n^{28}\text{D}$ 1.4234; d^{25} 0.831. Clarke reported b. p. 151° while Bodroux and Taboury[11] reported b. p. 151–153°; $n^{18}\text{D}$ 1.4286; d^{15} 0.830. Both methylisobutyl ketone (b. p. 118°) and methylisobutylcarbinol (b. p. 130°, less than 5%) were recovered.

Hydrogen 2,4-Dimethylhexyl-4-phthalate (II).—Over a period of one-half hour 130 g. of I was added to a vigorously stirred suspension of 39 g. of potassium sand in benzene (2.5 l.). After four hours the potassium had reacted and the clear solution was pumped under nitrogen pressure *into* a benzene (1.5 l.) solution of 148 g. of phthalic anhydride. After reacting overnight the thick mixture was poured into iced-water. Three sodium carbonate extracts of the benzene layer and the aqueous alkaline layer were acidified to liberate an oil which was extracted with benzene (phthalic acid remained insoluble). The benzene solution was extracted with three portions of 5% aqueous sodium carbonate, which were then acidified and extracted with ether. The dried (anhydrous sodium sulfate) ethereal solution was concentrated at the aspirator to give 275 g. of crude II. On the basis of the neutralization equivalent of 307 (calcd. for $C_{16}H_{22}O_4$, 278) the actual yield was 249 g., 90% of the theoretical value.

Addition of an excess of saturated aqueous barium chloride to a solution of 16 g. of crude II in 2% aqueous sodium hydroxide precipitated an oil which rapidly crystallized. The addition of pentane (4–5 volumes) to an ethereal (50 ml.) solution of this material induced crystallization. **Barium 2,4-dimethylhexyl-4-phthalate** crystallized as long, fibrous needles, m. p. 79–81° (after thorough drying *in vacuo* at room temperature, m. p. 84–86°).

Anal. Calcd. for $C_{32}H_{42}O_8Ba \cdot H_2O$: C, 54.13; H, 6.25; Ba, 19.35. Found: C, 54.38; H, 6.54; Ba, 18.94.

Resolution of Brucine 2,4-Dimethylhexyl-4-phthalate (III).—This salt crystallized when a solution of 352 g. of anhydrous brucine and 248 g. of racemic II in 535 ml. of acetone was allowed to stand overnight. A standard triangle-type fractional crystallization was carried out. The solutions in acetone, used in quantities just sufficient

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[9] This example illustrates the unique suitability of the infrared spectra as a means of establishing in general the structural identity of racemic and optically active modifications.

[10] All melting points are corrected.

[11] Bodroux and Taboury, *Compt. rend.*, **148**, 1678 (1909).

to effect solution at the boiling point, were allowed to crystallize overnight. Periodically the rotation of II obtained from the brucine salt in the usual way was measured in 95% ethanolic solution at concentrations of 5–10% in a Schmidt–Haensch instrument reproducible to ±0.01°. Strict adherence to the triangle scheme was interrupted when mother liquors failed to deposit crystalline material and whenever the head fraction became less than 20 g. (fourteenth crystallization in this case). At such times the head fraction was held until the optical purity of the succeeding fraction reached a value that allowed combination. In this way twenty recrystallizations of the head fraction afforded 26 g. of brucine (+)-2,4-dimethylhexyl-4-phthalate, $[\alpha]\mathrm{D}$ −4.8°; m. p. 142.5°.

Anal. Calcd. for $C_{39}H_{48}O_8N_2$: C, 69.62; H, 7.19; N, 4.16. Found: C, 69.91; H, 7.15; N, 4.11.

The rotation of the corresponding hydrogen phthalate was +7.3°. The change of m. p. of III and of rotation of corresponding hydrogen phthalate has been shown in Fig. 1. The solubility, operationally defined as the number of g. crystallizing at room temperature from 100 ml. of acetone saturated at the boiling point, changed from *ca.* 30 g. between the fourth to eighth crystallization to *ca.* 13 g. between the fourteenth to twentieth crystallization.

Mixtures of *r*-III (m. p. 140.5°) and resolved III (m. p. 142.5°) were melted despite the fact that slight decomposition prevented remelting of the mixtures. The resulting diagram showed a distinguishable minimum at 138° and at about equal parts of the two salts.

At the end of the resolution (a thirty-four-layer pyramid) the crystalline fractions were weighed and the rotations of the corresponding hydrogen phthalates were measured: 12.5 g. (+6.3°); 51 g. (+4.9°); 72 g. (+1.6°); 59.5 g. (+0.7°); 63 g. (−0.3°); 50 g. (−1.5°); 33.5 g. (−3.0°); 18.5 g. (−4.5°). Total recovery of *all* material was 90% (542 g.).

The non-crystalline material (26.5 g.) from the combined mother liquors on treatment with 32.5 g. of strychnine in 800 ml. of ethyl alcohol gave crystalline plates of **strychnine 2,4-dimethylhexyl-4-phthalate**, m. p. 177–177.5°. (The strychnine salt was of no use in continuing the resolution of (−)-II but did serve to remove impurities.)

Anal. Calcd. for $C_{37}H_{44}O_6N_2$: C, 72.52; H, 7.24; N, 4.57. Found: C, 72.45; H, 7.51; N, 4.77.

Regeneration gave optically impure (−)-II, $[\alpha]^{25}\mathrm{D}$ −4.8°.

Optically Active 2,4-Dimethylhexan-4-ol (I). (a) Lithium Aluminum Hydride.—To a solution of 3.5 g. of lithium aluminum hydride in 100 cc. of absolute ether was added a solution of 8.1 g. of (+)-hydrogen 2,4-dimethylhexyl-4-phthalate (+7.3°) in 100 cc. of absolute ether. After being stirred for one hour at room temperature, the mixture was treated with 50 cc. of water. Separation of the ether layer left a gummy residue which was thoroughly triturated with ether. The ethereal solution was washed with 2% aqueous sodium hydroxide and with water, dried with potassium carbonate and concentrated on the steam-bath. Distillation gave 2.4 g. of (−)-I: b. p. 152° (760 mm.), $n^{18}\mathrm{D}$ 1.4277; $[\alpha]^{21}\mathrm{D}$ −2.72° (α = −2.26°, neat, l = 1); $[\alpha]^{26}\mathrm{D}$ --2.72° (α = −4.52°, neat, l = 2); $[M]\mathrm{D}$ = −3.54°; $[\alpha]^{25}\mathrm{D}$ −3.5° (α = −0.30°, c = 8.50 in 95% ethanol, l = 1).

In this case the yield (63%) was lowered by a slight accident during concentration below the values of 80–85% usually obtained.

In a similar experiment (−)-II (−4.8°) was converted to (+)-I in 83% yield: b. p. 152°; $n^{25}\mathrm{D}$ 1.4246; $[\alpha]^{24}\mathrm{D}$ +1.55° (α = +2.58°, neat, l = 2); $[\alpha]^{24}\mathrm{D}$ +2.1° (α = +0.19, c = 9.10 in 95% ethanol, l = 1). From the distillation residue, phthalalcohol was isolated, m. p. 63.5–64.5°.

(b) **Ethylmagnesium Bromide.**—An ethereal (150 ml.) solution of 9 g. of (+)-II (+5.5°) was added to ethereal (100 ml.) ethylmagnesium bromide (from 20 ml. of ethyl bromide and 4.7 g. of magnesium). After two hours of refluxing, the mixture was hydrolyzed with saturated ammonium chloride. The resulting ether layer was extracted with 1% aqueous sodium hydroxide, washed with water, dried with potassium carbonate and concentrated *in vacuo*. Distillation at 12 mm. gave 2 g. of carbinol which, upon redistillation at 760 mm., gave some olefin, b. p. 112–115°, $[\alpha]\mathrm{D}$ 0°, and impure carbinol. Two additional distillations, one at 52 mm. (b. p. 78–80°) and the other at 760 mm. gave (−)-I: b. p. 152°; $n^{18}\mathrm{D}$ 1.4259; $[\alpha]^{27}\mathrm{D}$ −2.5° (α = −0.13°, c = 5.10 in 95% ethanol, l = 1).

Anal. Calcd. for $C_8H_{18}O$: C, 73.78; H, 13.93. Found: C, 73.55; H, 14.02.

A similar experiment using (−)-II (−2.7°) gave (+)-I, $[\alpha]^{27}\mathrm{D}$ +1.5° (α = +0.08°, c = 5.27 in 95% ethanol, l = 1).

Often dehydration accompanied the distillation of alcohol regenerated by the Grignard method.

Infrared Spectra.—The infrared spectra were measured for us by Dr. Abraham Savitsky in a Perkin–Elmer Infrared Spectrophotometer transformed by Professor Ralph S. Halford and Dr. Savitsky into a double beam instrument recording the per cent. transmission automatically. Unmodified tracings are reproduced in Fig. 2. The sample was contained in a sodium chloride cell which did not permit constant layer thickness. Details of the instrument are contained in the Doctoral Dissertation of Abraham Savitsky, Columbia University, 1949, and will be published.

Summary

Methylethylisobutylcarbinol, prepared from methyl isobutyl ketone and ethylmagnesium bromide, was reacted with phthalic anhydride *via* the potassium salt of the carbinol to form the hydrogen phthalate ester. From the combination of the hydrogen phthalate with brucine and the systematic fractional crystallization of this brucine salt from acetone, optically pure hydrogen (+)-2,4-dimethylhexyl-4-phthalate and partially resolved hydrogen (−) 2,4-dimethylhexyl-4-phthalate were obtained. Reductive cleavage of these acid phthalates with lithium aluminum hydride yielded optically pure (−)-2,4-dimethylhexan-4-ol and partially resolved (+)-2,4-dimethylhexan-4-ol. This is the first resolution of an aliphatic, tertiary alcohol in which the asymmetric, tertiary carbon atom bears the hydroxyl group.

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