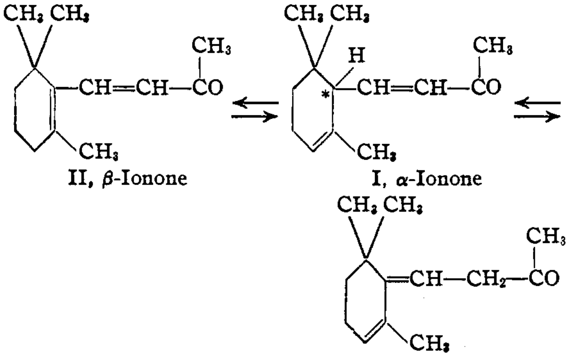
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, LABORATORIES OF THE MOUNT SINAI HOSPITAL]

Studies on Ionone. II. Optical Resolution of *dl*-α-Ionone[1]

BY HARRY SOBOTKA, EDITH BLOCH, H. CAHNMANN, EDITH FELDBAU AND EDITH ROSEN

The mechanism of racemization of optically active compounds involves in many instances the shift of a double bond, which results in the temporary removal of a hydrogen atom from the center of asymmetry; the return of the hydrogen atom to this center, when this shift is reversed, may lead with equal probability to the original configuration or to its mirror image. Such shifts may be achieved by enolization as in the case of acids of the $CR_1R_2H—COOH$ type through the intermediary formation of the symmetric form $CR_1R_2=C(OH)_2$.[2]

The carbon atom from which the side chain issues in α-ionone (I) is a center of asymmetry. It may temporarily lose its hydrogen atom by shifting of either the ethenoid bond in the nucleus or of that in the side chain. Any set of conditions, under which an equilibrium exists between α- and β-ionone, or between α-ionone and the isomeric ketone III may thus lead to the racemization of α-ionone. The observations reported in the preceding paper[3] suggest the probability under certain experimental conditions of shifts of the nuclear double bond from the β-ionone structure to the α-ionone structure. The rigor of such conditions and the likelihood of the shift may be gaged by the susceptibility of optically active α-ionone to racemization. We therefore undertook the resolution of *dl*-α-ionone into its optically active components. They may act as useful indicators for the instability of the double bond constellation in reactions involving ionone and its derivatives; moreover, the optical resolution of α-ionone is also of interest in view of the optical activity of α-carotene and other naturally occurring carotenoids, and because of its bearing on the relation between odor and molecular structure.



II, β-Ionone

I, α-Ionone

III, Isomeric ketone

The optical resolution of carbonyl compounds cannot be accomplished by the traditional Pasteur methods of salt formation with optically active acids or bases, nor by esterification with optically active acids as in the case of racemic alcohols. A partial resolution of *dl*-camphor by means of the formation of diastereomeric coördination compounds with the optically active desoxycholic acid was described by Sobotka and Goldberg.[4] In the case of racemic aldehydes, Sobotka and Rubin[5] succeeded in the preparation of the diastereomeric pair of Schiff bases of α-phenylpropanal with *d*-β-naphthol phenylaminomethane.[6] It was, however, impossible to regenerate from these compounds the enantiomeric forms of the aldehyde, because of their immediate racemization under the conditions of the hydrolytic scission of the Schiff bases; this racemization must be due to enolization to phenylvinyl alcohol in analogy to the racemization of carboxylic acids discussed above.

The use of optically active nitrogenous reagents for the resolution of racemic ketones has been described by several authors and was recently surveyed by Woodward.[7] The use of *l*-menthyl-N-aminocarbamate, "*l*-menthydrazide," introduced by these authors, appeared promising for the optical resolution of α-ionone. The formation of the diastereomeric mixture of *d*- and *l*-α-ionone-*l*-menthydrazones took place easily, but the mixture, though crystallizing well, was difficult to separate because of the slight differences in the solubilities of the components. The less soluble *levo*-derivative was obtained in very pure form after ten recrystallizations. The *dextro*-form of not quite maximal specific rotation was obtained in poorer yield after approximately twice as many recrystallizations.

When hydrolytic scission of the Schiff bases was carried out in the presence of ethanol according to Woodward, the liberated *l*-menthydrazide was further decomposed and the end-products were contaminated with free menthol. Hence, the regeneration of the ketones was carried out by steam distillation in aqueous medium in the presence of phthalic anhydride. The resulting *d*-α-ionone and *l*-α-ionone showed specific rotations of +347 and −406°. Their refractive indices agreed with that

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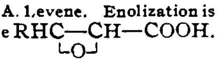
[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development, and The Mount Sinai Hospital.

[2] The presence of an H-atom on the α-carbon atom is a necessary but not a sufficient condition for enolization and racemization, as was pointed out to me by the late Dr. P. A. Levene. Enolization is *e. g.*, not possible in a glycidic acid of the type



$$\mathrm{RHC{-}CH{-}COOH}\ (\text{—O—})$$

—H.S.

[3] H. Sobotka, E. Bloch and D. Glick, THIS JOURNAL, **65**, 1961 (1943).

[4] H. Sobotka and A. Goldberg, *Biochem. J.*, **26**, 905 (1932).

[5] H. Sobotka and M. J. Rubin, unpublished experiments.

[6] M. Betti in "Organic Syntheses," Coll. Vol. 1, p. 372, John Wiley and Sons, New York, N. Y., 1932.

[7] R. B. Woodward, T. P. Kohman and G. Ch. Harris, THIS JOURNAL, **63**, 120 (1941).

of racemic α-ionone. There was a distinct difference in odor between the *d*- and the *l*-form.

Experimental

The *dl*-α-ionone used had been purified by repeated recrystallization of its semicarbazone until the refractive index $n^{23}\text{D} = 1.4995$.[8]

Preparation of *d*- and *l*-α-Ionone-*l*-menthydrazones.—Fifty-seven and six-tenths g. (0.3 mole) of *dl*-α-ionone was dissolved together with 64.2 g. (0.3 mole) of *l*-menthydrazide of $[\alpha]^{23}\text{D}$ −76.7° in 240 cc. of 95% ethanol, containing 2% of sodium acetate and 1% of acetic acid. After refluxing for two and one-half hours, 113 g. of a mixture of the diastereomers crystallized on cooling. The specific rotation of the mixture was about −20°, its m. p. 163–65°. Repeated fractional recrystallizations led to a product of $[\alpha]^{22}\text{D}$ −320° (in EtOH), m. p. 185°, and a more soluble fraction of $[\alpha]^{22}\text{D}$ +230° (in EtOH), m. p. 176° (calcd. for $C_{24}H_{40}O_2N_2$: N, 7.21. Found: N, 7.37).

Preparation of β-Ionone-*l*-menthydrazone.—The *l*-menthydrazone of β-ionone was prepared for comparison from a sample of β-ionone of $n^{22}\text{D}$ 1.5183. The specific rotation of the recrystallized product was −35°, m. p. 178°. As this value represents the contribution of the *l*-menthydrazone moiety to the specific rotation, a 1:1 mixture of *d*- and *l*-α-ionone-*l*-menthydrazone should approximate this value. Hence, the value of +230° for the dextrorotatory diastereomer is presumably *ca.* 20° too low in comparison with −320° for the levorotatory form. The higher purity of the *l*-compound accounts for the higher numerical value of the specific rotation for the resulting free *l*-α-ionone as compared with the *d*-enantiomer (see below).

Hydrolysis of Menthydrazones.—2.0 g. of purest *l*-α-ionone-*l*-menthydrazone was suspended with 4.5 g. of phthalic anhydride in 35 cc. of water and subjected to steam distillation for two and one-half hours. The distillate was thoroughly extracted with ether and 0.6 g. of an oil was obtained. Its $[\alpha]^{27}\text{D}$ showed the high value of −406°, its refractive index was $n^{25}\text{D}$ 1.5000. By the same procedure a dextrorotatory α-ionone was obtained from *d*-α-ionone-*l*-menthydrazone; its specific rotation $[\alpha]^{23}\text{D}$ was +347°, its $n^{22}\text{D}$ 1.5021.

2,4-Dinitrophenylhydrazones and *p*-Chlorobenzoylhydrazones of *l*- and *d*-α-Ionone.—Both optically active α-ionones were characterized by the preparation of the two derivatives. Their melting points are summarized below; N of dinitrophenylhydrazones of *d*-and *l*-α-ionone; Found: 15.3 and 15.2; calcd. 15.1.

TABLE I

Melting points, °C., of	*l*-α-Ionone	*d*-α-Ionone	*dl*-α-Ionone
2,4-Dinitrophenylhydrazone	133	129	143
p-Chlorobenzoylhydrazone	200–201	196–198	214

Summary

The resolution of *dl*-α-ionone was accomplished by means of *l*-menthydrazone. The use of optically active α-ionone as an indicator for the stability of the double bond system in ionone and its derivatives is discussed.

NEW YORK, N. Y.

RECEIVED JULY 6, 1943

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[8] We are greatly indebted to Dr. Ernest Theimer, Director of Research, Van Ameringen-Haebler Inc., Elizabeth, N. J., for supplying us with highly purified α-ionone and β-ionone.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

Synthesis of 16,17- and 17,18-Octadecenoic Acids[1,2]

BY ROLAND KAPP[3] AND ALEXANDER KNOLL[4]

Although several isomeric octadecenoic acids are known, the group is incomplete. The following reports the synthesis of two new members of this important group, and in addition two new keto-octadecenoic acids.

Three methods have been used in the preparation of long chain monoethenoid acids: the malonic ester synthesis, the Grignard synthesis and the acetoacetic ester synthesis.

The syntheses of the 16,17- and 17,18-octadecenoic acids were achieved by preparing the unsaturated keto acids by means of the acetoacetic ester method, followed by reduction of the keto acids by means of the Wolff–Kishner method to the respective olefinic acids.

The 17,18-octadecenoic acid was synthesized by the following procedure: 10,11-undecenoyl chloride was condensed with sodio-diethyl-acetyl suberate, whereupon α-acetyl-α-10,11-undecenoyl-diethyl suberate was formed. G. M. Robinson and R. Robinson[5] have pointed out that when two acyl groups occur in a compound such as (III), the acyl group derived from the stronger acid is preferentially removed by hydrolysis. Therefore, (III) was hydrolyzed by means of the stepwise procedure used by the Robinsons and their associates yielding (VI) 8-keto-17,18-octadecenoic acid. The keto acid (VI) was then reduced using the Wolff–Kishner method to (VII), 17,18-octadecenoic acid.

The synthesis of the 16,17-octadecenoic acid was achieved in the same general way using 9,10-undecenoyl chloride.

The position of the double bond in the 16,17- and 17,18-octadecenoic acids was proved by oxidation to the expected dicarboxylic acids, 1,14-tetradecamethylene dicarboxylic acid and 1,15-pentadecamethylenedicarboxylic acid. Both unsaturated acids absorbed two gram atoms of hydrogen and were converted thereby into stearic acid. The following diagram outlines the preparation of 17,18-octadecenoic acid.

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[1] From a dissertation submitted by R. Kapp to the Faculty of Pure Science, Columbia University, N. Y. C., in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[2] The authors are deeply indebted to Professor J. M. Nelson, Columbia University, for his encouragement and advice.

[3] Address: National Oil Products Co., Harrison, N. J.

[4] Address: Metals Disintegrating Co., Elizabeth, N. J.

[5] G. M. Robinson and R. Robinson, *J. Chem. Soc.*, **127**, 175 (1925).