chloride, benzenesulfonyl chloride, and phenyl isothiocyanate. The 4,6-dinitro-2-benzenesulfonamidophenylacetate* was prepared from the corresponding amine and benzenesulfonyl chloride in alkaline solution.

Summary

A number of new derivatives of picramic acid were prepared. Also several known derivatives were prepared by greatly improved processes. A study of the rearrangements of certain derivatives of picramic acid substantiated previous work on acyl-2-aminophenols. The error in the previously reported O-acetylpicramic acid is clarified.

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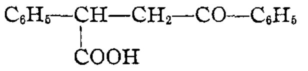
[CONTRIBUTION FROM THE THOMPSON LABORATORY OF THE PHILLIPS EXETER ACADEMY]

The Racemization of an Optically Active Acid and its Methyl Ester

BY C. L. BICKEL

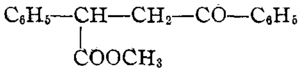
It is well known that optically active acids whose asymmetric carbon atom holds both a hydrogen and the carboxyl group, $\underset{\displaystyle CO_2H}{R—\underset{|}{C}H—R'}$, are racemized by bases with more difficulty than are their esters.[1–5] In all but one of the cases studied, the racemization of the ester was accompanied by hydrolysis. And in this one case,[3,4] although the rate of racemization of the ester was measured, the racemization of the acid was not studied quantitatively. In consequence it is impossible to compare, except in a qualitative way, the rates of racemization of an ester and the corresponding acid in any known instance.

The preparation and use of the active forms of β-benzoyl-α-phenylpropionic acid, I, in connection with another problem indicated that they are unusually stable in the presence of bases, no racemization being detected under ordinary conditions. On the other hand, the methyl esters, II, of the optically active forms of the acid are racemized with ease even in very dilute solutions of a base at room temperature.



$\underset{\displaystyle COOH}{C_6H_5—\underset{|}{C}H—CH_2—CO—C_6H_5}$

I



$\underset{\displaystyle COOCH_3}{C_6H_5—\underset{|}{C}H—CH_2—CO—C_6H_5}$

II

Concentrations of sodium hydroxide which produce measurable rates of racemization in methyl alcoholic solution do not cause any saponification of the ester. Under these conditions the only product is the inactive ester. Higher concentrations of sodium hydroxide, which racemize the active ester much too fast to make measurements possible, cause saponification of the ester. Concentrated aqueous sodium hydroxide, with enough added acetone to give solubility, saponifies the active esters with but partial racemization. This behavior agrees with that shown by the compounds studied by McKenzie[1,2] and by Wren.[3,4]

Basic solutions which racemize the active ester in a few minutes have no measurable effect on the active acid over a period of at least a month. A higher temperature and a more concentrated solution of the base are required to racemize the active acid at a rate which can be measured conveniently. In fact, hydrobromic acid or hydriodic acid seem to be as effective as sodium hydroxide in racemizing the active acid.

The fact that acids and bases seem to be equally effective in racemizing the active acid does not imply that the high temperature is solely responsible for the racemization. The active acid undergoes no racemization when held slightly above its melting point (181°) for some hours in a Pyrex melting point tube.

The rate of racemization of the active ester increases with an increase in the concentration of base. The rate of racemization of the active acid increases with an increase in the concentration of base and also increases with temperature. The effect of a change in temperature on the racemization of the active ester was not investigated.

No attempt has been made to draw any exact relationship between the concentration of base and the rate of racemization, since one case does not warrant a general conclusion. The facts are presented in the light of utility and it is hoped

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(1) McKenzie and Thompson, *J. Chem. Soc.*, **87**, 1019 (1905).
(2) McKenzie and Wren, *ibid.*, **115**, 602 (1919).
(3) Wren and Williams, *ibid.*, **109**, 576 (1916).
(4) Wren, *ibid.*, **113**, 213 (1918).
(5) Gadamer, *J. prakt. Chem.*, **195**, 389 (1913).

that the results may be of use to others in the future.

Experimental Part

McKenzie and Wren[6] found that there is considerable racemization of the menthyl esters of mandelic acid during alkaline hydrolysis. It is therefore inadvisable to adopt Hahn and Lapworth's[7] procedure of decomposing the quinine salts of the acid by means of sodium hydroxide. Dilute sulfuric acid was used instead, thus minimizing the chance of racemization of the esters.

Resolution of the *dl*-Acid, I.—Hahn and Lapworth first resolved β-benzoyl-α-phenylpropionic acid using quinine as the active base and ethyl acetate as the solvent. The same active base and the same solvent were used in this problem but the procedure has been standardized so much that it seems wise to give it in detail.

A boiling solution of 57 g. of quinine in 500 cc. of ethyl acetate is mixed with a boiling solution of 45 g. of the *dl*-acid in 300 cc. of ethyl acetate and the combined solution heated on the steam-bath for thirty minutes. During this period a solid begins to separate. The mixture is allowed to stand for one and one-half hours with frequent stirring by means of a stout glass rod. At the end of this period the separated solid has produced a very thick paste.

The solid (a) is filtered off and washed with 100 cc. of ethyl acetate.

The combined filtrates are allowed to stand overnight and any solid filtered off. This can be called solid (b).

The filtrate from solid (b) is concentrated to a very small volume, the ethyl acetate being recovered, and allowed to solidify. This is solid (c).

Each fraction of solid is worked up in the following way. The solid is shaken in a separatory funnel with ether and dilute sulfuric acid. The sulfuric acid takes up the quinine, leaving the acid in the ether. The acid is extracted from the ether by dilute sodium hydroxide solution and recovered by acidification of the alkaline solution. The quinine is recovered by pouring the sulfuric acid solution, with vigorous stirring, into a large excess of sodium hydroxide solution. Quinine precipitates out and can be collected.

The acid from each fraction of solid is fractionally crystallized from acetone.

Solid (a) gives about 12 g. of dextro acid, melting at 181° and having a molecular rotation in methyl alcohol of $[\alpha]^{26}\text{D}$ $+148°$.

Solid (b) is small and gives inactive acid.

Solid (c) gives about 12 g. of levo acid, melting at 181° and having a molecular rotation in methyl alcohol of $[\alpha]^{26}\text{D}$ $-148°$.

Esterification of the Levo Acid

1. **By Methyl Alcohol and Sulfuric Acid.**—A solution of 5 g. of the levo acid in 50 cc. of methyl alcohol containing 12.5 cc. of concentrated sulfuric acid was refluxed for three hours. Dilution with iced water followed by ether extraction gave an ether solution from which 0.05 g. of the levo acid was recovered by extraction with aqueous sodium bicarbonate. The ether solution yielded an oil which solidified after standing for some days in the refrigerator. The yield was 4.9 g.

The methyl ester of the levo acid crystallizes in large diamond plates from ether–petroleum ether and melts at 52°.

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.1; H, 6.01. Found: C, 75.9; H, 6.1.

2. **By Methyl Alcohol and Hydrobromic Acid.**—A solution of 1 g. of the levo acid in 40 cc. of methyl alcohol containing 10 cc. of 40% aqueous hydrogen bromide was refluxed for two hours. The yield of levo ester was 1 g.

3. **By Silver Oxide and Methyl Iodide.**—A solution of 1 g. of the levo acid in 40 cc. of anhydrous ether containing 2 g. of silver oxide (alkali free) and 4 g. of methyl iodide was refluxed for nine and one-half hours. A quantitative yield of the levo methyl ester was realized.

Hydrolysis of the Methyl Ester of the Levo Acid

1. **By Sulfuric Acid.**—One gram of the levo methyl ester was dissolved in a solution containing 2 cc. of sulfuric acid, 25 cc. of glacial acetic acid and 30 cc. of water. The solution was refluxed for two hours, diluted with iced water and extracted with ether. Sodium bicarbonate solution extracted an acid from the ether solution. The weight of the acid was 0.95 g. and a mixed melting point proved it to be the levo acid.

2. **By Aqueous Alkali.**—A solution of 1 g. of the levo methyl ester in 25 cc. of acetone and 25 cc. of 10% aqueous sodium hydroxide was heated on the steam-bath for fifteen minutes. Dilution with 200 cc. of iced water produced no precipitate. Acidification of the solution with hydrochloric acid gave more than 0.9 g. of β-benzoyl-α-phenylpropionic acid which melted from 150 to 175°. Polarimetric observation showed that the acid was about 50% racemized.

The methyl alcohol used in all subsequent work was carefully freed of traces of bases by distilling it from oxalic acid through a good column, then through an all Pyrex apparatus into a Pyrex receiving flask.

The polarimeter tubes used in this problem were of Pyrex with fused-in Pyrex optical windows and a T-inlet tube in the middle of the tube. Thus the solutions could come into contact with nothing but Pyrex glass.

The concentration of the sodium hydroxide in the solutions was determined by titration against a standard oxalic acid solution.

Racemization of the Levo Methyl Ester by Alcoholic Alkali.—Since a standard procedure was followed in all experiments involving the racemization of the levo methyl ester, this procedure is given and the results for the different experiments are presented in tabular form.

The methyl alcoholic solution of sodium hydroxide was placed in the polarimeter tube containing a weighed amount of the finely powdered levo ester. After complete solution of the ester, which in no case took longer than five minutes, the course of the racemization was followed by means of the polarimeter. At the end of the reaction the products were recovered from the solution and identified. In each case the total volume of solution in the tube was determined by weighing the tube filled with water to the same level as in the experiment.

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[6] McKenzie and Wren, *J. Chem. Soc.*, **117**, 680 (1920).

[7] Hahn and Lapworth, *ibid.*, **85**, 1355 (1904).

Concn. of levo ester in g. per 100 cc. of soln.	Normal concn. of NaOH[a]	Temp., °C.	Time required for 50% loss of activity	Product
3.0	0.38	26	<5 minutes	75% inactive ester 25% inactive acid
2.94	.051	26	1.3 hours	Inactive ester
3.23	.029	26	2.5 hours	Inactive ester
3.1	.014	26	5.0 hours	Inactive ester
2.79	.008	26	6.0 hours	Inactive ester
3.35	.0002	26	52.0 hours	Inactive ester

[a] Forty grams of sodium hydroxide in 1000 cc. of methyl alcohol solution is assumed to be 1 normal.

Racemization Experiments with the Levo Acid

1. In Aqueous Sodium Hydroxide at Room Temperature.—The standard procedure described previously under racemization of the ester was followed. The results can be presented most easily in tabular form.

Concn. of sodium hydroxide, *N*	Temp., °C.	Observation	Product
10	26	Sodium salt formed insoluble jelly in the tube	Levo acid
5	26	Sodium salt separated partially as oily drops No change in rotation	Levo acid
2.5	26	No change in rotation in one month	Levo acid
1	26	No change in rotation in one month	Levo acid

2. In Methyl Alcoholic Sodium Hydroxide at Room Temperature.—The standard procedure described above was followed. In a 0.4 *N* sodium hydroxide solution in methyl alcohol no change in the rotation of the levo acid could be detected in one month. The levo acid was recovered quantitatively.

3. In Boiling Aqueous Sodium Hydroxide.—The inconvenience of keeping a polarimeter tube and contents at a constant, elevated temperature made some modification of the procedure necessary. The following procedure was adopted.

An aqueous solution of the levo acid in sodium hydroxide, containing 0.5 g. of the levo acid per 25 cc. of solution, was refluxed, samples being removed at intervals by means of a pipet. After removal each sample was diluted with iced water, acidified with hydrochloric acid and the solid product collected on a sintered glass filter. The rotation of the solid product in methyl alcohol was then determined by means of the polarimeter.

Concn. of NaOH, *N*	Temp., °C.	Time required for 50% loss of activity	Product
1	101	Two hours	Inactive acid
0.5	100–101	Six hours	Inactive acid

4. In Boiling Methyl Alcoholic Sodium Hydroxide.—The procedure described in the preceding section was followed, substituting methyl alcohol for water.

Concn. of NaOH, *N*	Temp., °C.	Time required for 50% loss of activity	Product
2	65–66	6 hours	Inactive acid
1	65–66	20–25 hours	Inactive acid

5. In Boiling Hydrobromic Acid.—One-half gram of the levo acid was refluxed for two hours with 15 cc. of 40% hydrobromic acid. The resulting product was considerably racemized, both inactive acid and unchanged levo acid being present in the solid product. This reaction could not be studied in the polarimeter tube because traces of a very insoluble solid, probably a polymer of the acid, appeared and the resulting cloudiness made readings impossible.

6. In Boiling Hydriodic Acid.—One gram of the levo acid was refluxed for one hour with 20 cc. of hydriodic acid, sp. gr. 1.70. The levo acid gradually melted to a reddish oil. The product was the inactive acid. Therefore racemization was complete. This reaction could not be studied in the polarimeter tube because of insolubility of the material and because of the intense red color which developed in the solution.

Summary

Optically active β-benzoyl-α-phenylpropionic acid is particularly resistant to racemization by bases; the methyl ester of this acid is racemized quite easily by dilute bases with no accompanying hydrolysis.

The rates at which the acid and its ester are racemized are compared.

EXETER, N. H.

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