entropy of activation.[32-34] These are all compatible with a mechanism involving a quasi-cyclic intermediate as shown above. It is reasonable to assume that *o*-substituents of the types involved in these studies may retard the formation of such an O–H bond and, in so doing, stabilize these esters by preventing the formation of the postulated six-membered cyclic intermediate.

It is not particularly surprising, however, that the *o*-chloro and *o*-bromo groups actually affect this reaction in an anomalous fashion, for there are many examples of the well known proximity effect.[35] It is more surprising that the small *o*-fluoro group also demonstrates this same stabilization of the ester toward heat. The influence of an *o*-halogen may be caused by depolarization of the carbonyl group by the halogen, thus decreasing the attraction of a β-hydrogen to the carbonyl oxygen. A steric factor may explain the slight stabilizing influence of the *o*-methyl group.

When the characteristic temperatures of pyrolysis of esters were plotted as a function of their rates of hydrolysis in 85% ethanol, as shown in Fig. 2, a linear relationship was obtained for nearly all the benzoates including those substituted *ortho*. The relative rates of hydrolysis are reported by Ingold.[36] Apparently the proximity effect on the pyrolysis of esters is of the same order of magnitude as is the proximity effect on the rate of hydrolysis of esters.

As would be expected, esters with the greatest vibrational energy required higher temperatures to bring about their pyrolysis. This correlation is shown in Fig. 3. Although there is not ideal correlation between the characteristic temperature of pyrolysis and the O–C stretching of the infrared spectra of the esters, there is general agreement. The esters with the highest wave numbers also show the greatest stability to heat.

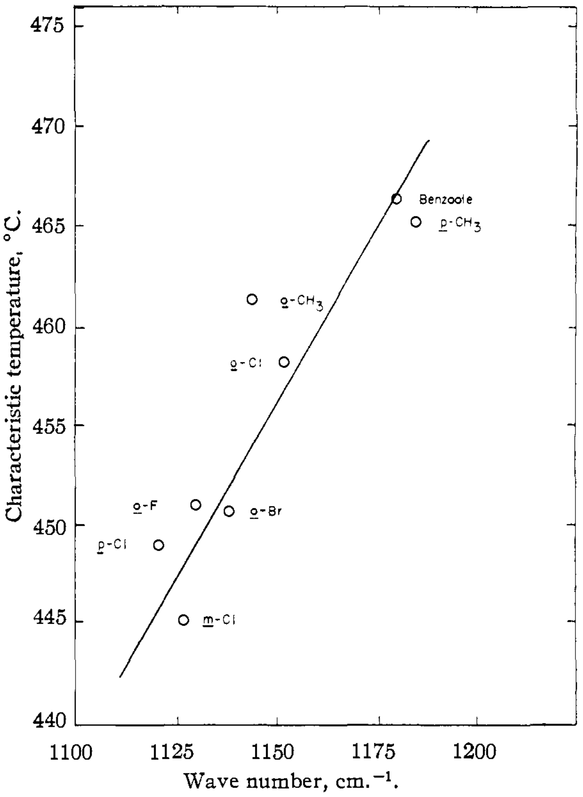

Fig. 3.—Plot of characteristic temperature *vs.* O–C stretching band in the infrared spectra of substituted cyclohexyl benzoates.

In order to relate the effect (if any) of *o*-substituents more quantitatively to the ease of ester pyrolysis, it will be necessary to determine the thermodynamic properties (energy and entropy of activation) by appropriate kinetic studies of various substituted benzoates. This method of relating entropy of activation to the *ortho*-effect is well known and will aid in the future study of the mechanism of the pyrolysis of esters.

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[32] A. T. Blades, *Can. J. Chem.*, **32**, 366 (1954).

[33] E. E. Sommers and T. I. Crowell, THIS JOURNAL, **77**, 5443 (1955).

[34] D. H. R. Barton, A. J. Head and R. J. Williams, *J. Chem. Soc.*, 1715 (1953).

[35] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 204.

[36] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," George Banta Publishing Co., 1st Ed., Menasha, Wisconsin, 1953, p. 759.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Stereochemical Course in the Alkylation of Phenylacetonitrile and Phenylacetic Acid with Optically Active α-Phenylethyl Chloride[1]

BY WILLIAM J. CHAMBERS, WALLACE R. BRASEN AND CHARLES R. HAUSER

RECEIVED AUGUST 6, 1956

Phenylacetonitrile and phenylacetic acid were alkylated with L(+)-α-phenylethyl chloride (I) to give *erythro*-D(+)-2,3-diphenylbutyronitrile (II) and *erythro*-D(−)-2,3-diphenylbutyric acid (III), respectively. In both alkylations an optically active asymmetric center has been produced. The effect of temperature on the observed rotation of optically active α-phenylethyl chloride has been measured.

Recently potassiophenylacetonitrile prepared by means of potassium amide in liquid ammonia was alkylated with racemic α-phenylethyl chloride to give a 99% yield of the higher melting diastereomeric pair of 2,3-diphenylbutyronitrile (equation 1).[2] This racemic modification has been shown to be the *erythro* form.[3]

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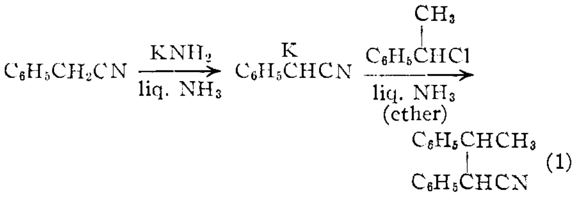
[1] Supported by the National Science Foundation.

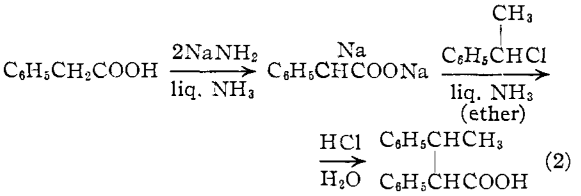
[2] C. R. Hauser and W. R. Brasen, THIS JOURNAL, **78**, 494 (1956).

[3] W. R. Brasen and C. R. Hauser, *ibid.*, **79**, 395 (1957).



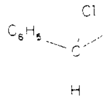
$$C_6H_5CH_2CN \xrightarrow[\text{liq. NH}_3]{\text{KNH}_2} C_6H_5\overset{K}{C}HCN \xrightarrow[\substack{\text{liq. NH}_3\\ \text{(ether)}}]{C_6H_5\overset{CH_3}{C}HCl} \begin{matrix} C_6H_5CHCH_3 \\ | \\ C_6H_5CHCN \end{matrix} \quad (1)$$

Similarly, the disodio salt of phenylacetic acid prepared by means of two equivalents of sodium amide in liquid ammonia was alkylated with racemic α-phenylethyl chloride to give a 74% yield of the *erythro* form of diphenylbutyric acid (equation 2).[4]



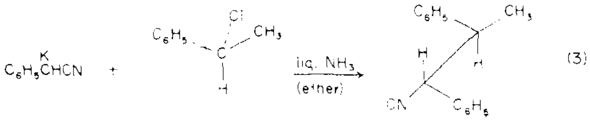
$$C_6H_5CH_2COOH \xrightarrow[\text{liq. NH}_3]{2NaNH_2} C_6H_5\overset{Na}{C}HCOONa \xrightarrow[\substack{\text{liq. NH}_3\\ \text{(ether)}}]{C_6H_5\overset{CH_3}{C}HCl} \xrightarrow[H_2O]{HCl} \begin{matrix} C_6H_5CHCH_3 \\ | \\ C_6H_5CHCOOH \end{matrix} \quad (2)$$

In the present investigation the stereochemical courses of these alkylations were studied. Optically active α-phenylethyl chloride was prepared from optically active α-phenylethyl alcohol[5] by a modification of the method of Burwell, Shields and Hart.[6] Instead of introducing free hydrogen chloride into the reaction mixture containing the optically active alcohol, the ester was first prepared from the alcohol and phosphorus oxychloride, and dry pyridine hydrochloride then added. In this manner consistent results were obtained. There was isolated a 62% yield of optically active α-phenylethyl chloride having an observed rotation of +96.4° at 24.6° when corrected to optically pure α-phenylethyl alcohol. The configuration of (−)-α-phenylethyl chloride has been related to D(+)-glyceraldehyde[7]; therefore the chloride used in this study was L(+)-α-phenylethyl chloride (I).



I

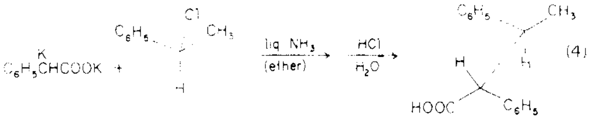
Potassiophenylacetonitrile was alkylated with I (α^{26} D+90.21°) to give an 88% yield of *erythro*-D(−)2,3-diphenylbutyronitrile (II) which was optically active ($[\alpha]^{26}$ D−24° in benzene). The absolute configuration of the product is based on the assumption that inversion occurs at the asymmetric carbon of I.[8] The reaction may be represented by equation 3.



I II

Since only the *erythro* modification of II was obtained and because it was optically active (one of the enantiomorphs), an optically active asymmetric carbon has been produced.

Similarly dipotassiophenylacetic acid was alkylated with I (α^{25} D+84.32°) to give an 86% yield of *erythro*-D(+)-2,3-diphenylbutyric acid (III) which was optically active ($[\alpha]^{26}$ D+25.5° in absolute ethyl alcohol).[9] Again basing the absolute configuration of the product on the assumption that inversion occurs at the asymmetric carbon of I,[8] the reaction may be represented by equation 4. Since the product was of the *erythro* form and was optically active (one of the enantiomorphs), an optically active asymmetric carbon has been produced.



I III

The reason why only the *erythro* form of the nitrile is obtained in such alkylations in liquid ammonia is not entirely clear. The *threo* form might also be produced in an approximately equal amount[10] and then converted in the reaction mixture to the *erythro* isomer.[11] If so this conversion must be rapid and essentially complete. Thus, it was observed earlier[3] that racemic *threo*-2,3-diphenylbutyronitrile is converted completely to the *erythro* isomer within ten minutes by a catalytic amount of potassiophenylacetonitrile in liquid ammonia.

A second possibility might be that the carbanion reacts as if it had a preferred configuration to produce exclusively the *erythro* form of the product, thereby generating directly the optically active asymmetric carbon. However, there appears to be no precedent for such a reaction of a carbanion.

In connection with the present work, the rotational values of the optically active α-phenylethyl chloride were observed to change with variations in temperature. Thus, lowering the temperature from 30.1 to 18.8° resulted in an increase in the observed rotation from 77.1 to 80.6°. The results of the readings at different temperatures are given in Table I. Pickard and Kenyon[12] have reported a similar influence on the rotational values of optically active α-phenylethyl alcohol.

Experimental[13]

Optically Active α-Phenylethyl Alcohol.—Commercial racemic α-phenylethyl alcohol was resolved by the method of Downer and Kenyon[5] through fractional crystallization of the half ester of the phthalic acid–brucine salt. The

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[4] C. R. Hauser and W. J. Chambers, THIS JOURNAL, **78**, 4942 (1956).

[5] E. Downer and J. Kenyon, *J. Chem. Soc.*, 1156 (1939).

[6] R. L. Burwell, A. D. Shields and H. Hart, THIS JOURNAL, **76**, 908 (1954).

[7] H. Hart and E. Eleuterio, *ibid.*, **76**, 516 (1954); see also W. Klyne, "Progress in Stereochemistry," Academic Press, Inc., New York, N. Y., 1954, p. 177.

[8] R. L. Letsinger (THIS JOURNAL, **70**, 406 (1948)) has presented evidence that inversion occurs in the SN2 type of displacement when optically active 2-bromobutane is treated with sodium benzyl.

[9] Attempts to resolve racemic *erythro*-2,3-diphenylbutyric acid in order to ascertain the amount of optical activity retained in the alkylation were only partially successful. Three recrystallizations of the brucine salt of the racemic acid from 75% ethyl alcohol and water gave an acid having a rotation of $[\alpha]^{22}$D +18° in absolute ethyl alcohol. Further recrystallizations did not increase the amount of rotation.

[10] Actually the two isomers have been obtained in approximately equal amounts from the alkylation of potassiophenylacetonitrile with racemic α-phenylethyl chloride in ether; ref. 2.

[11] In this event the optically active asymmetric carbon may be considered to be produced indirectly by the subsequent conversion of the threo isomer to the *erythro* form.

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

[13] Boiling points and melting points are uncorrected.

TABLE I

INFLUENCE OF TEMPERATURE ON THE OBSERVED ROTATION OF OPTICALLY ACTIVE α-PHENYLETHYL CHLORIDE

T, °C.	α_{D}	T, °C.	α_{D}
30.1	77.1	24.7	78.7
27.5	77.8	23.6	79.2
26.8	78.0	22.7	79.3
26.3	78.2	22.0	79.6
25.7	78.4	20.5	80.1
25.0	78.6	18.8	80.6

active alcohol had a boiling point of 80–80.5° at 5.6 mm., $n^{25}\mathrm{D}$ 1.5264. The rotational value for optically pure α-phenylethyl alcohol is taken as $\alpha^{25}\mathrm{D}$ 43.7°.[6]

Optically Active α-Phenylethyl Chloride (I).—This compound was prepared by a modification of an earlier procedure.[6]

In a 500-ml. three-necked flask equipped with a sealed stirrer, a low temperature thermometer, a drying tube and an addition funnel was placed 47.5 g. (0.6 mole) of dry pyridine, 24.3 g. (0.2 mole) of optically active α-phenylethyl alcohol ($\alpha^{25}\mathrm{D}$ −38.24°, 1 dm., neat) and 200 ml. of dry chloroform. The mixture was cooled to −13° in a Dry Ice–methanol-bath, and 30.7 g. (0.2 mole) of phosphorus oxychloride was added as rapidly as possible with stirring, keeping the temperature of the reaction mixture below −9°. The resulting mixture was stirred for 5 min. at −9 to −13°, and a solution of 0.8 mole of dry pyridine hydrochloride in approximately 150 ml. of dry chloroform was added, maintaining the same temperature range. After warming for 3 hr. at 40 ± 3° the reaction mixture was decomposed by shaking with crushed ice for 5 min. and the two layers then separated. The chloroform layer (with which was combined two 25-ml. chloroform extracts of the aqueous layer) was washed with two 25-ml. portions of 85% phosphoric acid, followed by ice-water, and dried over anhydrous sodium sulfate at 0° for 30 min., then overnight with Drierite at 0°. The solvent was removed *in vacuo* at approximately 27°, and the residue fractionally distilled to give 17.5 g. (62%) of L(+)-α-phenylethyl chloride, b.p. 53–54° at 4.3 mm., $n^{25}\mathrm{D}$ 1.5247, $\alpha^{24.6}\mathrm{D}$ +84.31° (1 dm., neat); corrected to optically pure alcohol, $\alpha^{24.6}\mathrm{D}$ +96.4°.

α-Phenylethylation of Phenylacetonitrile with I.—To a stirred solution of 0.101 mole of potassium amide in 600 ml. of liquid ammonia was added 12.0 g. (0.102 mole) of phenylacetonitrile in 15 ml. of anhydrous ether, followed after 5 min. by 14.1 g. (0.1 mole) of α-phenylethyl chloride ($\alpha^{26}\mathrm{D}$ +90.21°) in 15 ml. of anhydrous ether (added during 15 min.). After one hour, the liquid ammonia was replaced by ether, and 100 ml. of 1.5 N hydrochloric acid added to the reaction mixture. The ether was removed by distillation and the solid collected on a funnel. The solid was washed with water and then dissolved in acetone. Ethanol was added, and most of the acetone distilled. After cooling the solution overnight in the refrigerator there was precipitated 15.2 g. (88%) of *erythro*-D(−)-2,3-diphenylbutyronitrile (II), $[\alpha]^{26}\mathrm{D}$ −24° (c 2 in benzene). The product melted at 134.5–135°; reported m.p. for the racemate is 132.5–133.5°.[2]

α-Phenylethylation of Phenylacetic Acid with I.—To a stirred solution of 0.11 mole of potassium amide[14] in 400 ml. of liquid ammonia was added 7.5 g. (0.055 mole) of phenylacetic acid, followed by 7.0 g. (0.05 mole) of α-phenylethyl chloride ($\alpha^{25}\mathrm{D}$ +84.31°) in 10 ml. of anhydrous ether. The reaction mixture was stirred for 1 hr. The liquid ammonia was evaporated on the steam-bath and ether added. The ethereal mixture was filtered, and the solid dissolved in water. After filtering, the aqueous solution was acidified to precipitate 10.3 g. (86%) of *erythro*-D(+)-2,3-diphenylbutyric acid (III), m.p. 170–180°. After one recrystallization from a mixture of ether and petroleum ether the acid melted at 185–186°, $[\alpha]^{26}\mathrm{D}$ +25.5° (c 4 in absolute ethanol); reported[4] m.p. for the racemate 187–187.5°.

Influence of Temperature on the Observed Rotation of Optically Active α-Phenylethyl Chloride.—A water-jacketed 1-dm. polarimeter tube was filled with optically active α-phenylethyl chloride ($\alpha^{25}\mathrm{D}$ +78.6°). The desired temperature for each reading was obtained by changing the temperature of the water in a large bath which was connected to the polarimeter tube jacket through a circulating pump. The results are given in Table I.

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[14] See R. S. Yost and C. R. Hauser, THIS JOURNAL, **69**, 2325 (1947).

DURHAM, NORTH CAROLINA

[CONTRIBUTION FROM THE COLLEGE OF CHEMISTRY AND PHYSICS, THE PENNSYLVANIA STATE UNIVERSITY]

Chemistry of Enolates. I. The Kinetics and Mechanism of Alkylation of Alkyl Phenyl Ketones[1]

BY HARRY D. ZOOK AND WILLIAM L. RELLAHAN[2]

RECEIVED SEPTEMBER 10, 1956

Alkylations of sodium enolates prepared from eight primary and secondary alkyl phenyl ketones have been measured kinetically. Homogeneous solutions of the enolates in ether were obtained quantitatively from the ketones and sodium triphenylmethide. By varying the length of the alkyl chain from methyl to octyl, a maximum rate of ethylation was found with propiophenone. A marked decrease in rate accompanied branching on the α-carbon atom of the ketone. Alkylation of butyrophenone by various alkyl bromides gave the following rate sequences: methyl > ethyl > n-propyl > isobutyl >> neopentyl and ethyl > isopropyl < t-butyl. The rate of alkylation was a function of the concentration of sodium enolate for all alkylations, including alkylations by t-butyl bromide and benzyl chloride. The mechanism of the reaction involves a transition state which has both S$_{\mathrm{N}}$1 and S$_{\mathrm{N}}$2 character. Association of two molecules of the sodium enolate of butyrophenone in 0.07–0.13 M ethereal solutions is indicated by ebulliometric measurements.

The two-stage alkylation of ketones by a strong base such as sodamide[3] or sodium alkoxide[4] and an alkyl halide is a well known synthetic process. The ketones first are converted to the corresponding sodium enolates, and the latter compounds react metathetically with the alkylating agents. The reaction mechanism is generally considered to involve carbanions, although there is no evidence that the intermediate sodium enolates are dissociated under the conditions employed. These studies were undertaken to investigate the nature of the enolate and the mechanism of its alkylation.

Phenyl alkyl ketones were converted to sodium

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[1] Taken in part from a Ph.D. thesis submitted by William L. Rellahan to the Graduate School of The Pennsylvania State University, August, 1956.

[2] Du Pont Postgraduate Teaching Assistant, 1955–1956.

[3] F. W. Bergstrom and W. C. Fernelius, *Chem. Revs.*, **12**, 106 (1933); A. Haller, *Bull. soc. chim.*, [4] **31**, 1073 (1922).

[4] G. Vavon and J. M. Conia, *Compt. rend.*, **223**, 157, 245 (1946); J. M. Conia, *Ann. chim.*, **8**, 709 (1953).