

The clear solution was extracted with twelve portions (30 ml. each) of ethyl acetate. The extract was dried over calcium sulfate, filtered and evaporated and the residue was crystallized from water to give 0.3 g. of the ketoacid XIVb, m.p. 165–166° dec. The ketoacid was converted to the characteristic oxime (*vide supra*), m.p. 255–256° dec. The infrared spectrum of the oxime (KBr disk) was identical with that of an authentic sample.

Oxidation of XVIIb to XIVb.—A solution of 1.75 g. of potassium dichromate in 40 ml. of water containing 6 g. of concentrated sulfuric acid was added in one portion with stirring to 1.5 g. of XVIIb. The temperature was held at 30–40° for 2 hours, the reaction mixture was diluted with water to a volume of 100 ml. and, after standing overnight

at 5°, it was extracted with ten 45-ml. portions of chloroform. This extract gave a negligible quantity of product. The aqueous solution was further extracted with ten 45-ml. portions of ethyl acetate, the extract was dried over calcium sulfate, filtered and evaporated. The residue was crystallized from water (using charcoal) to give 1.0 g. of XIVb, m.p. 165–166° dec. This sample of ketoacid gave oxime of m.p. 257–258° dec.

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Studies of Stereospecificity in the α -Phenylethylation of Phenylacetonitrile and Phenylacetic Acid and of Epimerization of the Alkylation Products¹

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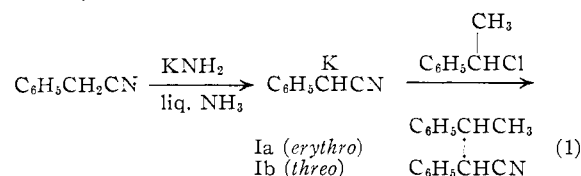
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The α -phenylethylation of potassio-phenylacetonitrile with α -phenylethyl chloride affords exclusively the *erythro* isomer of 2,3-diphenylbutyronitrile under certain conditions, but a mixture of the two diastereoisomers under certain other conditions. No conclusion is warranted concerning stereospecificity since relatively rapid epimerization of one or both of the diastereoisomers of the alkylation product may mask the primary reaction. Conditions were developed for effecting partial epimerization of the *erythro* or *threo* isomer and complete epimerization of the *threo* isomer. The α -phenylethylation of disodio- or dipotassio-phenylacetic acid with α -phenylethyl chloride in liquid ammonia affords largely the *erythro* isomer of 2,3-diphenylbutyric acid. Since the *threo* isomer is not epimerized appreciably under similar conditions, this alkylation is considered to follow a stereospecific course. The *threo* isomer of 2,3-diphenylbutyric acid was prepared satisfactorily by the acid hydrolysis of the corresponding *threo*-nitrile.

The α -phenylethylation of phenylacetonitrile² and phenylacetic acid³ with α -phenylethyl chloride has been effected recently by means of alkali amides in liquid ammonia to produce excellent yields of the *erythro* isomers⁴ of 2,3-diphenylbutyronitrile² and 2,3-diphenylbutyric acid, respectively.

The indicated stereospecificity of these reactions as well as the possible epimerization of the diastereoisomers of the alkylation products has now been studied.

α -Phenylethylation of Phenylacetonitrile.—This reaction was effected through potassio-phenylacetonitrile which was prepared by means of an equivalent of potassium amide in liquid ammonia (equation 1).



The relative proportions of the diastereoisomers of 2,3-diphenylbutyronitrile (Ia) and (Ib) afforded by this reaction are dependent on the solvents employed in the alkylation step. Thus, it was reported previously,² and confirmed in the present investigation, that the *erythro* isomer is obtained exclusively when the alkylation is effected in liquid ammonia containing a little ether, whereas approximately equal yields of the two isomers are realized when the reaction is carried out in ether alone. Under

the former condition, the *erythro* isomer is obtained as a precipitate, while under the latter, both isomers remain in solution although a precipitate of potassium salts is present. In line with the latter result, it was found that roughly equal yields of the two isomers are also produced when the alkylation is effected in liquid ammonia containing sufficient tetrahydrofuran to keep both isomers in solution. These results are summarized in Table I.

TABLE I

DIASTEREOISOMERS OF 2,3-DIPHENYLBUTYRONITRILE FROM α -PHENYLETHYLATION OF POTASSIOPHENYLACETONITRILE

Media solvents	State of reaction mixture	Diastereoisomers, yield, %	
		<i>erythro</i> (Ia)	<i>threo</i> (Ib)
Liq. NH ₃ (little ether)	Heterogeneous ^a	99	0
Ether alone	Heterogeneous ^b	30	29
Liq. NH ₃ and tetrahydrofuran	Homogeneous ^b	43	33

^a *Erythro* isomer precipitates. ^b Both isomers remain in solution.

These results may or may not represent the proportions of the isomers produced in the alkylation step proper. Thus, the exclusive production of the *erythro*-nitrile in the first experiments in Table I might have involved the primary formation of both isomers accompanied by the complete epimerization of the *threo*-nitrile, since the latter isomer has been observed⁴ to undergo such a complete epimerization under similar conditions in the presence of potassio-phenylacetonitrile which is the reactive intermediate in the alkylation. Moreover, the production of the two isomers in the second and third experiments in Table I might have involved the primary formation of only the *erythro* or the *threo*

(1) Supported by the National Science Foundation.

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

(3) C. R. Hauser and W. J. Chambers, *ibid.*, **78**, 4942 (1956).

(4) See W. R. Brasen and C. R. Hauser, *ibid.*, **79**, 395 (1957).

isomer accompanied by its partial epimerization, since such partial epimerizations to give equilibrium mixtures of the two isomers has been shown to occur under similar conditions. These epimerizations are further considered below.

At the present time no conclusion is warranted concerning the stereospecificity of the alkylation, since relatively rapid epimerizations may mask the primary reaction.

Epimerization of Diastereoisomers of 2,3-Diphenylbutyronitrile.—When kept in solution in the presence of a catalytic amount of a suitable base, each of the isomers of this nitrile underwent partial epimerization to produce an equilibrium mixture of the two isomers. These results are summarized in Table II. For convenience only the *erythro* isomer (m.p. 133–134°) usually was isolated although the *threo* isomer, which is a liquid or low melting solid (m.p. 35–36°),⁵ was indicated to be present in the reaction products. That this is indeed a true indication of the isomer distribution is indicated by the finding that a blank experiment, in which a 1:1 mixture of the two isomers was subjected to the isolation procedure, led to the recovery of 88% of the solid (*erythro*) nitrile.

TABLE II

BASE-CATALYZED PARTIAL EPIMERIZATIONS OF DIASTEREOMERS OF 2,3-DIPHENYLBUTYRONITRILES IN SOLUTION

Starting isomer	Base	Solvent	Time, min.	<i>erythro</i> isomer yield, % ^a	Temp., °C.
<i>erythro</i>	KNH ₂	NH ₃ /THF ^b	0.3	53	-33
<i>threo</i>	KNH ₂	NH ₃ /THF ^b	0.3	53	-33
<i>erythro</i>	KNH ₂	NH ₃ /THF ^b	20	51	-33
<i>threo</i>	KNH ₂	NH ₃ /THF ^b	20	53	-33
<i>erythro</i>	KNH ₂	Ether	120	44	35
<i>threo</i>	KNH ₂	Ether	120	48	35
<i>erythro</i>	KOC ₂ H ₅	Ethanol	60	47	78
<i>erythro</i>	Piperidine	Pyridine	2 wk.	47	25
<i>threo</i>	Piperidine	Pyridine	2 wk.	47	25

^a Only higher melting isomer was isolated. ^b Tetrahydrofuran.

It can be seen from Table II that the partial epimerization of each of the isomers of 2,3-diphenylbutyronitrile occurred readily.⁶ Thus, their equilibrations by means of a catalytic amount of potassium amide were evidently established within 20 seconds in liquid ammonia and tetrahydrofuran at -33° and within 2 hours in ether at room temperature.⁷

Similarly the equilibration was brought about by means of a catalytic amount of potassium ethoxide in refluxing ethanol within 2 hours, and even by a mixture of pyridine and piperidine at room temperature within 2 weeks.

These equilibrations are useful for the preparation of the *threo*-nitrile from the *erythro* isomer which may be obtained quantitatively by the α -phenylethylation of potassium phenylacetone nitrile in liquid ammonia. This method is probably to be pre-

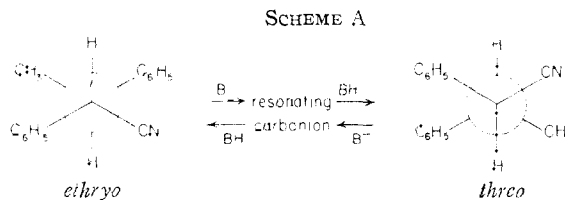
(5) The *threo* isomer has been crystallized only with difficulty; see ref. 2.

(6) At least certain of these equilibrations could probably be established within less time than indicated in Table II.

(7) Although potassium amide is only slightly soluble in ether, the isomeric nitriles are readily soluble in this solvent.

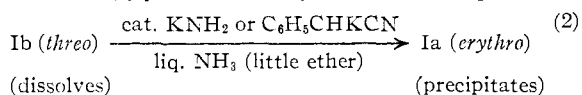
ferred to that involving the direct α -phenylethylation of potassium phenylacetone nitrile in ether, which produces relatively low yields of the two isomers.

The mechanism for these partial epimerizations presumably involves the ionization of the α -hydrogens of the *erythro*- and *threo*-nitriles by the base to form a common intermediate carbanion through which the equilibration is established (Scheme A).



In Scheme A the more favorable conformation of each of the isomers is represented employing Newman's notation.⁸ The fact that approximately equal amounts of the two nitriles were obtained under the conditions indicated in Table II shows that there is no great difference in the stabilities of the two isomers, or at least that the difference is not sufficient to be reflected in such equilibrations.

Although the base-catalyzed epimerization of each of the isomers of 2,3-diphenylbutyronitrile in solution produced approximately equal amounts of the two isomers (Table II), the essentially complete epimerization of the *threo*-nitrile to the *erythro* isomer was realized in the presence of a catalytic amount of potassium amide (or potassium phenylacetone nitrile)⁴ in liquid ammonia in which the latter isomer is relatively insoluble. Thus, the *threo*-nitrile⁵ readily dissolved in this solvent containing a little ether, and there precipitated within 10 minutes a 95% yield of the *erythro* isomer (equation 2).



While this result is to be ascribed merely to differences in the solubilities of the two isomeric nitriles, it is an interesting example of an essentially complete epimerization.

It should be mentioned that, whereas the *threo*-nitrile Ib readily undergoes partial or complete epimerization in the presence of bases, this isomer can be hydrolyzed by means of dilute sulfuric acid without appreciable isomerization to form a good yield of the corresponding *threo*-2,3-diphenylbutyric acid. In fact this hydrolysis has furnished the only good method for preparing the *threo*-acid (see next section).

Stereospecific α -Phenylethylation of Phenylacetic Acid.—This alkylation was effected through disodio-³ or dipotassium phenylacetic acid which was prepared by means of two equivalents of the corresponding alkali amide in liquid ammonia (equation 3).

The *erythro* isomer of 2,3-diphenylbutyric acid (IIa) was mainly obtained as reported earlier,³ and a little of the *threo* isomer of this acid IIb also was isolated by careful fractionation of the crude alkylation product. The yields of these two isomers in a typical experiment are given above in equation 3.

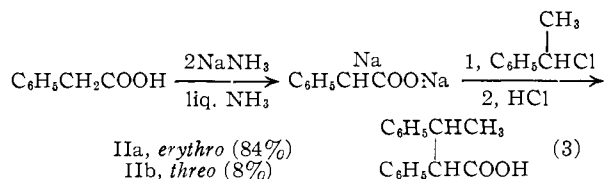
(8) M. S. Newman, *J. Chem. Educ.*, **32**, 344 (1955).

TABLE III
DATA FOR ISOMERS OF 2,3-DIPHENYLBUTYRIC ACID FROM α -PHENYLETHYLATION OF DISODIO- AND DIPOTASSIOPHENYLACETIC ACID

Di-alkali salt	Time, min.	Alkylation product, yield, %	erythro isomer (IIa)		threo isomer (IIb)		Ratio IIa/IIb
			yield, %	M.p., °C. ^a	Yield, %	M.p., °C. ^b	
Sodium	20	96	82.0	186-187	9.4	126-129 ^c	8.7
Sodium	20	94.5	80.2	182-184	3.1	117-122	
			3.5	177-184	4.7	125-128	10
Potassium	30	65.3	56.8	184-187	4.7	121-126	12
Potassium	90	80.0	69.1	185-187	6.9	120-124	
			2.2	183-186			10

^a Lit.³ m.p. 187-187.5°; m.p. 186°, A. A. Plentl and M. T. Bogert, THIS JOURNAL, 63, 909 (1941). ^b Lit. m.p. 135°, Ramart-Lucas, Ann. chim. phys., [8] 30, 424 (1913); m.p. 130-133° from hydrolysis of *threo*-nitrile (see Experimental). ^c Mixed m.p. with authentic *threo*-acid (m.p. 130-133°) was 126-129°.

In Table III are summarized the results from two alkylations each of the disodio and dipotassio salts of phenylacetic acid with α -phenylethyl chloride.



It can be seen from Table III that the ratio of the *erythro*-acid IIa to the *threo* isomer IIb produced in accordance with equation 3 was about ten to one.⁴ Evidently disodiophenylacetic acid underwent the alkylation faster than the dipotassio salt. Thus, although the concentrations of the reactants were the same in the four experiments listed in Table III, the alkylation of the disodio salt was essentially complete within 20 minutes whereas that of the dipotassio salt was incomplete even after 90 minutes. Since both salts appeared to be equally soluble and no appreciable β -elimination was observed, the faster rate with the former salt seems to be ascribable to the influence of the metallic cation.

The predominant formation of the *erythro* isomer of 2,3-diphenylbutyric acid evidently arises from a stereospecific α -phenylethylation of the carbanion of the dialkali salt of phenylacetic acid, and not from a possible subsequent epimerization of the alkylation product involving ionization of the α -hydrogen. Thus, the *threo* isomer of this acid (or more accurately its alkali salt) was not converted appreciably to the *erythro* isomer under conditions similar to those employed in the alkylation reaction (see equation 3) or even under more drastic conditions. Neither was the *erythro* isomer isomerized appreciably under such conditions. In Table IV are summarized the results obtained in attempted isomerization of each of the isomers of 2,3-diphenylbutyric acid in the presence of significantly more than one equivalent of a base, an equivalent of the base being neutralized in the ionization of the carboxyl hydrogen. Similar results were obtained when only one equivalent or slightly more than one equivalent of the base (alkali amide) was used.

It can be seen from Table IV that, in each case, the starting isomer was largely recovered after standing for various lengths of time with excess of alkali amide in liquid ammonia in homogeneous or heterogeneous media or with potassium ethoxide in ethanol solution. The conditions employed in most

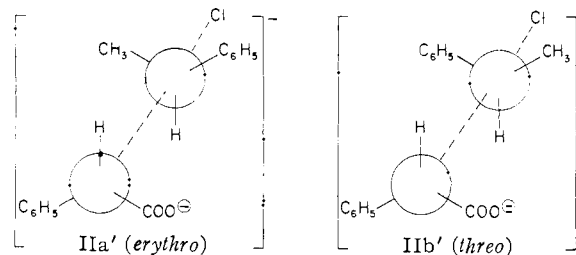
TABLE IV
ATTEMPTED EPIMERIZATION OF *threo* AND *erythro*-2,3-DIPHENYLBUTYRIC ACID

Starting isomer	Base	Equivalents	Solvent	Time, min.	Rec. isomer	M.p., °C.	Yield, %
<i>threo</i> ^a	KNH ₂	1.5	Liq. NH ₃ ^c	10	<i>threo</i>	127-130	93
<i>threo</i> ^a	KNH ₂	1.5	Liq. NH ₃ ^c	30	<i>threo</i>	125-129	92
<i>erythro</i> ^b	KNH ₂	2.0	Liq. NH ₃ ^c	420	<i>erythro</i>	186-188	87 ^e
<i>threo</i> ^a	KNH ₂	2.0	Liq. NH ₃ ^c	30	<i>threo</i>	127-130	94
<i>erythro</i> ^b	NaNH ₂	2.0	Liq. NH ₃ ^d	30	<i>erythro</i>	183-188	96
<i>threo</i> ^a	NaNH ₂	2.0	Liq. NH ₃ ^d	420	<i>threo</i>	127-129	98
<i>erythro</i> ^b	KOEt	1.3	EtOH ^e	1440	<i>erythro</i>	185-189	98
<i>threo</i> ^a	KOEt	1.3	EtOH ^e	1440	<i>threo</i>	125-130	94

^a M.p. 130-133°; prepared from hydrolysis of *threo*-nitrile (see Experimental). ^b M.p. 184-186°. ^c Sufficient solvent was employed to maintain solution. ^d Incomplete solution. ^e Methyl iodide was added at the end of the experiment; the material of m.p. 186-188° represents 98% of the acid isolated.

of these experiments may be considered to be somewhat more drastic than those used in the α -phenylethylation of the dialkali salt of phenylacetic acid in liquid ammonia (see equation 3), in which the medium was heterogeneous.

A possible explanation of the predominant formation of the *erythro* isomer is that the alkylation, which presumably involves the S_N2 type of displacement mechanism, has a more favorable transition state (with fewer non-bonding interactions) leading to this isomer than to the *threo* isomer. The transition states may be assumed to have conformations similar to those of the alkylation products as represented by IIa' and IIb' for the *erythro* and *threo* isomers, respectively.



It should be pointed out that, although no appreciable epimerization was realized in the experiments listed in Table IV, a little of the *threo*-acid might have been converted to the *erythro* isomer under these conditions since the melting point of the recovered *threo*-acid was usually somewhat lower than that of the starting *threo* isomer. Moreover, the melting point of the recovered *erythro*-acid was

generally slightly higher than that of the starting *erythro* isomer.

The fact that, in contrast to the isomers of 2,3-diphenylbutyronitrile, the isomers of 2,3-diphenylbutyric acid are not epimerized readily in the presence of an excess of amide ion is not entirely clear. One would certainly expect the α -hydrogen to be ionized since the corresponding proton of the phenylacetate ion is very readily removed under these conditions (see equation 3). In line with this a slight color was produced when the butyric acid was treated with amide ion; this color was, however, discharged by the addition of less than one-twentieth of an equivalent of methyl iodide (see note *e* of Table IV). If it is assumed that this color is indeed due to ionization, it is difficult to see why even after several hours the extent of isomerization should be negligible, since the carbon that loses a proton by the same process presumably loses its asymmetry.

Experimental⁹

α -Phenylethylation of Phenylacetonitrile.—This alkylation was effected under three sets of conditions, the results being summarized in Table I. The first two procedures were described previously.² The third procedure is described below.

To a solution of 11.7 g. (0.10 mole) of phenylacetonitrile and 14.0 g. of α -phenylethyl chloride in 2 l. of liquid ammonia containing 800 ml. of dry tetrahydrofuran there was added, over the period of 1 hr., 0.10 mole of potassium amide in 250 ml. of liquid ammonia. When the addition was complete, a small amount of ammonium chloride was added and the ammonia evaporated on the steam-bath. After filtering, the solution was concentrated to 100 ml. *in vacuo* and then diluted with water. The resulting oily solid was separated by filtration and washed with petroleum ether (b.p. 30–60°) to yield 4.64 g. of the *erythro* isomer of 2,3-diphenylbutyronitrile, m.p. 132–136°.

The aqueous organic washes were extracted well with ether, and the solvent removed to leave an oil which was distilled at 3.5 mm. There were obtained at this pressure 2.92 g. of starting halide, b.p. 50–52°; 5.34 g. of phenylacetonitrile, b.p. 82–84.5°; and 4.87 g. of a mixture of the *erythro* and *threo* isomers of 2,3-diphenylbutyronitrile, b.p. 154–158°. Treatment of this mixture with petroleum ether gave an additional 0.91 g. of the *erythro*-nitrile, m.p. 129–131°. The total yield of this isomer based on the amount of phenylacetonitrile used minus that recovered was 43%. The *threo*-nitrile was recovered as a liquid⁵ on removing the petroleum ether; yield 33%.

Partial Epimerizations of Diastereoisomers of 2,3-Diphenylbutyronitrile.—Partial epimerization of each of the isomers of this nitrile to form an equilibrium mixture of the two isomers was brought about under several sets of conditions as described below. The results are summarized in Table II.

(A) **With Potassium Amide in Liquid Ammonia and Tetrahydrofuran.**—In a typical experiment 2.33 g. (0.010 mole) of the *erythro*- or *threo*-nitrile was dissolved in 200 ml. of liquid ammonia containing 100 ml. of tetrahydrofuran. In an attached inverse addition flask, potassium amide was prepared from 0.10 g. (0.0025 mole) of potassium metal and 300 ml. of liquid ammonia. The base was run into the solution of the nitrile as quickly as possible. At the end of the desired reaction time the base was destroyed with ammonium chloride. The ammonia was removed on the steam-bath, the tetrahydrofuran solution concentrated and then diluted with water. The resulting oily crystals were filtered, washed with water and then with petroleum ether. Recrystallization from ethanol afforded *erythro*-nitrile, m.p. 133–135°.

(9) All melting points are uncorrected and recorded as observed on a Fisher-Johns melting point block.

In a blank experiment, a mixture of 1.16 g. each of the *erythro*- and *threo*-nitrile was treated exactly as above, except that in this case no potassium amide was added. Following the workup described above there was obtained 1.02 g. (88%) of the *erythro*-nitrile, m.p. 134.5–136°.

(B) **With Potassium Amide in Ether.**—Ether (400 ml.) was added to 0.008 mole of potassium amide in liquid ammonia, and the resulting solution heated on the steam-bath. When ammonia-free ether started to distil, 9.32 g. (0.04 mole) of the appropriate isomer of the nitrile was added to the reaction mixture. After a reflux period of 2 hr., the base was destroyed with water and ammonium chloride. The organic layer was separated and then washed with water. The residue that remained when the solvent was removed was treated as above to afford 4.07 g. of the *erythro*-nitrile, m.p. 132–134°.

(C) **With Potassium Ethoxide in Ethanol.**—The *erythro*-nitrile was dissolved in ethanol containing a 10–20 mole per cent. of potassium ethoxide and, after refluxing 2 hr., the solution was worked up to give both the *erythro* and *threo* isomers.

(D) **With Piperidine and Pyridine.**—A solution of the *erythro*- or *threo*-nitrile in approximately an equivalent of piperidine and a large excess of pyridine was allowed to stand for 2 weeks, and then worked up.

Complete Epimerization of *threo*- to *erythro*-Nitrile.—A sample of the liquid *threo*-nitrile in a little ether was added to 10 mole per cent. of potassium amide in liquid ammonia. After 10 min., the reaction mixture was worked up to give a 95% yield of the *erythro* isomer, m.p. 131–133°.

α -Phenylethylation of Phenylacetic Acid.—Solid phenylacetic acid (3.15 g., 0.023 mole) was added to 0.05 mole of sodium amide or alternately potassium amide in 300 ml. of liquid ammonia. The dark green reaction mixture was stirred for 5 min. and then 3.52 g. (0.025 mole) of α -phenylethyl chloride was added slowly. The resulting pea-soup-like mixture was stirred for the appropriate length of time and finally neutralized with ammonium chloride. The colorless suspension was evaporated to dryness on the steam-bath and the residual solid dissolved in 5% aqueous potassium hydroxide. The product obtained on acidification of the alkaline solution was collected by filtration and fractionally crystallized from aqueous ethanol. The results are summarized in Table III.

Attempted Isomerization of *threo*- and *erythro*-2,3-Diphenylbutyric Acid (Table IV). (A) **In Liquid Ammonia.**—In a typical experiment 3.0 g. (0.022 mole) of the *threo*-acid was added to a solution of 0.025 mole of potassium amide (prepared from 1 g. of potassium metal) in 300 ml. of liquid ammonia. The resulting suspension of white solid in the greenish liquid was stirred for the appropriate length of time and the base destroyed with an excess of ammonium chloride. The reaction mixture was then subjected to the same workup as the alkylation product described above. The solid which was obtained was recrystallized from aqueous ethanol to yield 2.83 g. of acid, m.p. 127–129°.

(B) **With Potassium Ethoxide in Ethanol.**—A solution of 0.50 g. (0.013 mole) of potassium and 2.4 g. (0.01 mole) of the *erythro*-acid in 50 ml. of ethanol was allowed to stand for 24 hours at room temperature. The solution was then poured into 600 ml. of ice-water and 50 ml. of concentrated hydrochloric acid. The precipitate was collected on a filter and dried to give 2.35 g. (98%) of starting material, m.p. 185–189°. Similar treatment of the 1.2 g. of the *threo* isomer afforded 1.13 g. of starting material, m.p. 125–130°.

Hydrolysis of *threo*-2,3-Diphenylbutyronitrile to the *threo*-Acid.—A solution of the *threo*-nitrile and 10 ml. of 50% aqueous sulfuric acid in 30 ml. of acetic acid was heated at reflux for three days. The cooled solution was poured into 400 ml. of water. The gummy precipitate was taken into ether, which was then washed with 5% aqueous sodium hydroxide. The solid obtained on acidification of the alkaline solution was recrystallized from aqueous ethanol to yield 6.27 g. (84%) of *threo*-2,3-diphenylbutyric acid, m.p. 130–133°.

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