[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Five- *vs.* Six-membered Ring Formation in the Cyclization of 2,3,4-Triphenylbutyric Acid; the Relative Importance of Stereochemistry[1]

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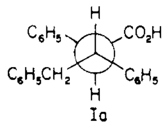
It has been found that the cyclization of each of the isomers of 2,3,4-triphenylbutyric acid by means of hydrogen fluoride yields 2-phenyl-3-benzylindanone as well as the expected 2,3-diphenyltetralone. The ratio of the two ketones depends on the configuration of the starting acid, since the low melting isomer leads mainly to the indanone and the high melting form gives mainly the tetralone. The structure of the indanone was proved by its conversion to 1-phenyl-2-benzylindene, which was shown to be identical to an authentic sample of that compound prepared by another route.

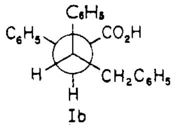
It is well known, largely as a result of the work of von Braun and co-workers,[2] that a six-membered ring will generally be formed in preference to a five-membered ring in the Friedel–Crafts type cyclization of aryl substituted acids. For example, the treatment of the acid chloride of either 2-benzyl-4-phenylbutyric acid or that of 2-benzylsuccinic acid with aluminum chloride affords exclusively the tetralones.[3] Recently a deviation of this rule was reported by Badger,[4] who showed that the anhydride of 2,3-diphenylglutaric acid (representing a single diastereoisomer), cyclizes to an indanone, rather than to the expected tetralone.

We have now found that each of the pure diastereoisomers of 2,3,4-triphenylbutyric acid is cyclized by means of hydrogen fluoride to a mixture of the corresponding indanone and tetralone. The ratio of five- to six-membered ring closure depended on the isomer of the acid used in the reaction.

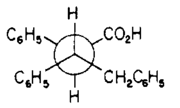
An examination of the Newman projection formulas of the two isomers of this acid suggests that these may indeed show different modes of cyclization. Though the preferred conformation of *threo*-2,3,4-triphenylbutyric acid (II) has the carboxyl group in a position favorable for the formation of a six-membered ring, the carboxyl in the preferred conformation of the other isomer (Ia) is in a position to form an indanone. In order to form a tetralone, I has to assume a conformation in which all the large groups are in interference (Ib).[5] If on the other hand the course of the reaction were decided at some later stage, Ib would lead to the *cis*-tetralone IIIb, and Ia to the *trans*-substituted indanone IIIa in which the large groups are less crowded than in the tetralone. If then these steric factors play an appreciable role in this reaction one would be led to predict that the *threo* isomer would produce the tetralone, and the *erythro* isomer the indanone.



Ia

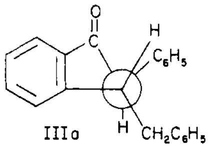


Ib

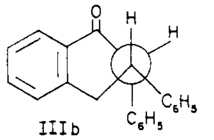


II

erythro *threo*



IIIa



IIIb

Preparation of Starting Materials.—The known isomer of 2,3,4-triphenylbutyronitrile[6] was equilibrated with a catalytic amount of potassium ethoxide in ethanol solution. Fractional crystallization afforded the known nitrile, m.p. 131°, and its isomer,[7] m.p. 88°, in roughly equal amounts. Hydrolysis of each of these nitriles under acidic conditions yielded the corresponding acids. It is of interest that when the reaction was stopped after 15 hours the amides were obtained. When basic hydrolysis was employed each of the nitriles gave the higher melting acid. These results are summarized in Scheme A.

SCHEME A

$$\begin{tikzcd}
\text{nitrile, m.p. } 131^\circ \arrow[r, shift left] \arrow[d, "H^+"'] \arrow[dr, "OH^-"] & \text{nitrile, m.p. } 88^\circ \arrow[l, shift left] \arrow[d, "OH^- \text{ or } H^+"] \\
\text{acid, m.p. } 141^\circ & \text{acid, m.p. } 159^\circ
\end{tikzcd}$$

For preparative purposes the two isomeric acids were both obtained from the higher melting of the nitriles, by the use of either basic or acid hydrolysis. In this way the fractionation was avoided.

Formation of Indanone from the Low Melting Acid.—Treatment of the acid m.p. 141° with liquid hydrogen fluoride afforded an 85% yield of neutral material. The infrared spectrum of the crude product exhibited bands at both 5.82 and 5.93 μ. The former was suggestive of the indanone IV, since the model compound V was found to have a single band at 5.85 μ. The band at 5.93 μ was presumably due to the tetralone VI (see below).

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[1] Supported by the Office of Ordnance Research, U. S. Army.

[2] See J. v. Braun and G. Manz, *Ann.*, **468**, 258 (1929), and W. S. Johnson, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 116, for lead references.

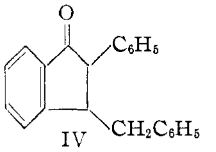
[3] J. v. Braun, *Ber.*, **61**, 441 (1928).

[4] G. M. Badger, J. E. Campbell and J. W. Cook, *J. Chem. Soc.*, 1084 (1949); another apparent exception to the rule has been reported by C. Ivanov and L. Mladenova-Orlinova, *Bull. inst. chim. acad. bulgare sci.*, **2**, 137 (1953) (*C. A.*, **49**, 6183f (1955)), no details of this work are available however.

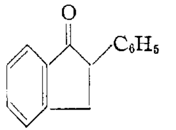
[5] The carboxyl group is referred to as the attacking group only for the sake of simplicity; its steric nature is assumed to be of the same nature as that of the reactive complex.

[6] Prepared by a procedure which will be published by C. R. Hauser, C. F. Hauser and P. J. Hamrick.

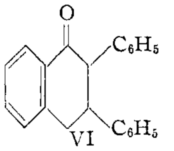
[7] This isomeric nitrile has been reported to melt at 190°, Y. De Schuttenbach, *Ann. chim.*, [11] **6**, 90 (1936); this product, however, was not fully characterized.



IV



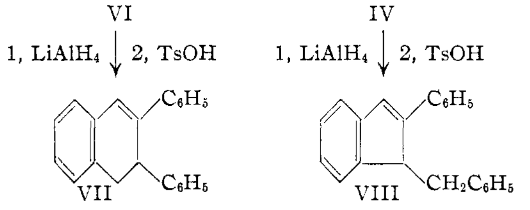
V

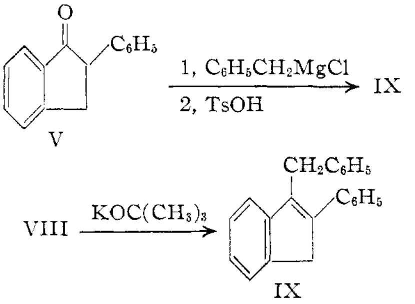


VI

Isolation of the presumed indanone presented some unusual difficulties, since it apparently has almost the same solubility characteristics as the tetralone. Thus, both fractional crystallization and chromatography failed to effect any noticeable separation. Since IV forms plates and VI heavy rods, mechanical separation finally was adopted. Pure samples of the indanone (λ_{max} 5.82 μ) and the known[8] tetralone (λ_{max} 5.93 μ) thus were obtained.

The possibility remained of course that IV was the diastereoisomer of the tetralone VI. Accordingly, each of the cyclization products was reduced to the corresponding alcohol with lithium aluminum hydride and these products were dehydrated by means of acid. The tetralone VI by this procedure afforded the known[9] compound VII while IV gave an olefin, VIII, that was different from but isomeric with VII. Since by this series of reactions one of the optical centers (and with it the possibility of diastereoisomers) had been destroyed, the carbon skeletons of IV and VI must be different. That IV did indeed possess a five-membered ring was shown by the scheme





The reaction of 2-phenylindanone with benzylmagnesium chloride afforded an alcohol which was dehydrated without further purification. The olefin obtained in this manner has been tentatively assigned the structure IX, although the double bond could be exocyclic. When the isomeric indene VIII was treated with potassium *t*-butoxide in butanol there was isolated from the reaction mixture a solid which proved identical to IX. The yield of isomerized indene was rather low (25%, crude), but this is not surprising since authentic IX after similar treatment was recovered in a yield of only 50%.

Cyclization Results.—Each of the isomers of the acid (I and II) was subjected to treatment with liquid hydrogen fluoride; its corresponding acid chloride was treated with stannic chloride in refluxing benzene. In all cases the total crude neutral product was examined by infrared spectroscopy. The proportion of indanone to tetralone was estimated from the ratio of the carbonyl band intensities by means of a series of spectra of mixtures of known proportions of pure IV and VI. In all cases the band at 5.93 μ was shown to be due to the tetralone by isolation of this compound. The results are shown in Table I.

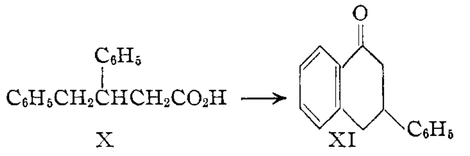
TABLE I

RATIO OF FIVE- TO SIX-MEMBERED RING CLOSURE FROM THE CYCLIZATION OF 2,3,4-TRIPHENYLBUTYRIC ACID

Starting acid, m.p., °C.	Cyclizing agent	Relative proportion of Tetralone VI	Indanone IV
141	HF	1	2
159	HF	3	1
141[a]	$SnCl_4$	6	1
159[a]	$SnCl_4$	20	<1

[a] Acid used to prepare the acid chloride.

It thus appears that the relative stereochemistry of the starting acid does exert an influence on the direction of ring closure. This effect is most pronounced in liquid hydrogen fluoride, where in going from one isomer to the other the ratio of ketones obtained is almost reversed. That this is not entirely a reagent effect, is shown by the fact that X, whose acid chloride is reported to yield exclusively XI with aluminum chloride, shows the same reaction in hydrogen fluoride. Though X differs from the acids used in the present work only by the absence of one phenyl group, the spectrum of the crude reaction product of 3,4-diphenylbutyric acid with hydrogen fluoride, revealed not a trace of indanone.



The last experiment in Table I represents those conditions under which the cyclization of 2,3,4-triphenylbutyric acid has been carried out previously.[8] Though no indanone could be isolated, the infrared spectrum does show a shoulder at 5.82 μ indicative of a trace of this isomeric ketone.

Though the relative configuration of the two starting acids is not known, enough evidence is at hand from the hydrolytic data of the nitriles to permit a tentative assignment. The fact that the acid of m.p. 159° was obtained as the exclusive product from either isomer of the corresponding nitrile indicates that this is the more stable of the two diastereomers. Similarly, Crawford[10] found that alkaline hydrolysis of XII afforded predominantly that isomer of XIII which on reduction[11] gave the m.p. 159° isomer of the triphenylbutyric acid.

An examination of molecular models suggests that the *threo* is the more stable of the two isomers,

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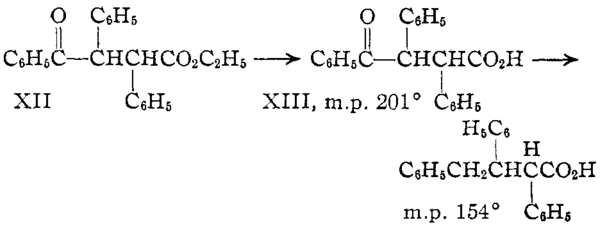
[8] F. Bergman, D. Schapiro and H. E. Eschinazi, THIS JOURNAL, **64**, 559 (1942).

[9] H. M. Crawford and H. B. Nelson, *ibid.*, **68**, 134 (1946).

[10] H. M. Crawford, *ibid.*, **60**, 3078 (1938).

[11] H. M. Crawford, *ibid.*, **61**, 608 (1939).

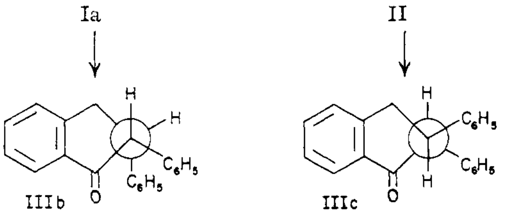


$$\underset{\text{XII}}{C_6H_5\overset{\overset{O}{\|}}{C}-\overset{\overset{C_6H_5}{|}}{C}H\underset{\underset{C_6H_5}{|}}{C}HCO_2C_2H_5} \longrightarrow \underset{\text{XIII, m.p. }201^\circ}{C_6H_5\overset{\overset{O}{\|}}{C}-\overset{\overset{C_6H_5}{|}}{C}H\underset{\underset{C_6H_5}{|}}{C}HCO_2H} \longrightarrow \underset{\text{m.p. }154^\circ}{C_6H_5CH_2\overset{\overset{H_5C_6}{|}}{C}H\overset{H}{\underset{\underset{C_6H_5}{|}}{C}}CO_2H}$$

since in the least crowded conformation the largest group (benzyl) is placed next to the smallest one (carboxyl; see Ia and II above). The acid of m.p. 159° would thus be assigned the *threo* configuration.

These assignments of configuration are also in line with the cyclization results, for the isomer which would be expected to yield mainly the indanone is the *erythro*, or according to the above assignments, the lower melting isomer.

It should be noted that, though each of the acids should lead to a different isomer of the tetralone, in fact only one was isolated. This could be accounted for by assuming that the acid first isomerizes, and thus all the indanone arises from one isomer of the acid and all the tetralone from the other. When, however, the cyclization of the low melting acid with stannic chloride was stopped short of completion, the recovered acid was essentially unchanged. It is of course possible that acid which leads to the tetralone is consumed as fast as it is formed, and thus the recovered acid would still be unisomerized. An alternate explanation for the formation of a single tetralone would be that produced from the low melting acid IIIb is isomerized to the more stable *trans*-configuration IIIc under the conditions of the reaction.



IIIb IIIc

By placing alkyl groups rather than aryl groups in the α-position of the butyric acids the possibilities for isomerization should be decreased. In this way some of the finer details of these cyclizations may be elucidated.

Experimental[12]

Isomerization of 2,3,4-Triphenylbutyronitrile.—To a cold solution of 0.28 g. (0.0061 mole) of potassium in 230 ml. of absolute ethanol there was added 13.5 g. of the high melting nitrile.[6] After 25 min. the reaction mixture was poured onto 2 l. of ice, and the resulting precipitate collected by filtration. This solid was recrystallized from 200 ml. of ethanol to yield 6.60 g. of nitrile, m.p. 124–130°. Further crystallization from the same solvent raised the m.p. to 130–132°, lit.[7] 129–131°.

The addition of water to the mother liquor of the crude nitrile obtained above afforded 6.00 g. of the other isomer as a solid, m.p. 82–84°. A small sample was recrystallized in high boiling (60–90°) petroleum ether to a constant m.p. of 85–87°.

Anal. Calcd. for $C_{22}H_{19}N$: C, 88.85; H, 6.44; N, 4.71. Found: C, 88.74; H, 6.41; N, 5.03.

Conversion of the Nitrile to 2,3,4-Triphenylbutyric Acid. (a) Alkaline Hydrolysis.—A suspension of 5.0 g. (0.017 mole) of the high melting nitrile and 5.0 g. of potassium hydroxide in 50 ml. of ethylene glycol was brought to reflux. Slow evolution of ammonia was noted from the resulting solution. After a heating period of 15 hr. the solution was poured into water. The resulting clear solution was washed with ether, filtered and finally acidified. The precipitate was recrystallized from ethanol to yield 4.7 g. (89%) of the acid, m.p. 159–160°, lit. 153–154°,[11] 158°.[8] One gram (0.003 mole) of the low melting nitrile was treated in the same manner to yield 0.88 g. (83%) of the acid, m.p. 159–160°.

(b) **Acid Hydrolysis.**—A solution of 6.93 g. (0.023 mole) of the high melting nitrile and 14 ml. of 50% sulfuric acid in 70 ml. of glacial acetic acid was heated under reflux for three days. At the end of this time, the reaction mixture was diluted with water and the solid extracted with ether. The ethereal solution was then washed with water, and the acid removed with 5% aqueous potassium hydroxide. Acidification of the alkaline solution afforded a solid, m.p. 131–135°. This was recrystallized from ethanol to afford 6.4 g. (88%) of acid, m.p. 137–140°, lit.[7] 138°. Under identical conditions, 2.5 g. of the low melting nitrile yielded 1.5 g. (57%) of acid, m.p. 152–155°.

(c) **Incomplete Acid Hydrolysis.**—A sample of the nitrile (5.0 g., 0.017 mole) of the high melting acid was hydrolyzed as above. In this case the reaction was diluted with water at the end of 15 hr. The solid which came out was collected by filtration and recrystallized twice from ethanol to afford 3.40 g. (64%) of the amide as fine needles, m.p. 168–171°. A sample was recrystallized from ethanol to a constant m.p. of 172–173°.

Anal. Calcd. for $C_{22}H_{21}NO$: C, 83.77; H, 6.71; N, 4.44. Found: C, 81.91; H, 7.45; N, 4.31.

The low melting nitrile (2.5 g., 0.008 mole), when subjected to the same conditions afforded the isomeric amide (2.0 g., 78%) as tiny flakes, m.p. 173–175°.

Anal. Calcd. for $C_{22}H_{21}NO$: C, 83.77; H, 6.71, N, 4.44. Found: C, 83.42; H, 6.79; N, 3.98.

The melting point of an intimate mixture of the two amides was 154–164° (s. 145°).

Cyclization of the Low Melting Acid with Hydrogen Fluoride.—To 200 ml. of well-stirred (magnetically) liquid hydrogen fluoride, 5.0 g. (0.016 mole) of the acid was added in portions over a period of 40 min. When all the liquid had evaporated, the residue was taken up in ether and this solution washed consecutively with water, saturated aqueous sodium bicarbonate and again water. The solution was then dried over sodium sulfate; the solvent was evaporated to leave behind 4.36 g. (92%) of gummy solid. The infrared spectrum of this solid showed bands at both 5.82 and 5.93 μ, the former being far more intense.

The solid was then recrystallized from ethanol until the crystals which came out were well formed. In this way 3.50 g. of the mixture was obtained. The flaky plates of the indanone IV were then separated mechanically from the stout prisms of tetralone VI.[13]

The indanone was recrystallized from ethanol to yield glistening scales, m.p. 97–99°. The infrared spectrum of this showed only the band at 5.82 μ.

Anal. Calcd. for $C_{22}H_{18}O$: C, 88.56; H, 6.09. Found: C, 88.58; H, 6.11.

Two recrystallizations of the other fraction gave the tetralone, m.p. 147–149°, lit.[8] 146–147°. The mixed m.p. of this with tetralone obtained from the cyclization of the high melting acid by the literature procedure[8] was 148–149°.

Conversion of the Indanone IV to 2-Phenyl-3-benzylindene (VIII).—A solution of 1.10 g. (0.0036 mole) of IV in 100 ml. of ether was added (10 min.) to a well-stirred suspension of 0.55 g. of lithium aluminum hydride in 25 ml. of ether. The suspension was maintained at a gentle reflux for 4 hr. and then allowed to cool. The excess reagent was decomposed with 4 ml. of water, and the resulting clear ether layer decanted from the solid. The latter was dissolved in dilute hydrochloric acid and this solution extracted with ether. The combined ethereal solutions were washed

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(12) All melting points are recorded as obtained on a Fisher-Johns melting point block. All analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(13) This procedure was rendered somewhat easier by the fact that the plates tend to cling to rough paper while the prisms roll off.

with water, percolated through anhydrous sodium sulfate and taken to dryness to leave behind a clear gum.

A solution of the crude alcohol in 30 ml. of benzene was heated under reflux in a flask equipped with a Dean–Stark trap until no more water came off. At this point 0.10 g. of *p*-toluenesulfonic acid was added to the reaction. The immediate evolution of water was noted. After two hours of heating, the solution was cooled, washed with saturated aqueous sodium bicarbonate and then water. The solvent was removed *in vacuo,* to leave behind a gum which solidified on scratching. This was recrystallized from methanol to yield 0.71 g. (66%) of the indene, m.p. 91–97°. A sample was further recrystallized from the same solvent to afford fine fibrous needles, m.p. 96–98°.

Anal. Calcd. for $C_{22}H_{18}$: C, 93.57; H, 6.43. Found: C, 93.50; H, 6.49.

1-Phenyl-2-benzylindene (IX). (a) **From 2-Phenylindanone.**—A solution of 8.73 g. (0.037 mole) of 2-phenylindanone[14] in 125 ml. of ether was added to 0.075 mole of benzylmagnesium chloride (prepared from 9.45 g. of benzyl chloride and 1.80 g. of magnesium) in 60 ml. of ether over a period of 15 min. The addition was accompanied by gentle refluxing. After an additional 4 hr. of heating, water and then ice-cold dilute hydrochloric acid were added to the reaction mixture. The ether layer was separated, washed to neutrality with water and dried over anhydrous sodium sulfate. An extremely viscous oil remained when the solvent was removed.

A solution of the product of the Grignard reaction in 90 ml. of benzene was heated under reflux in a flask equipped with a Dean–Stark trap until no more water came off. At this time 0.40 g. of *p*-toluenesulfonic acid was added to the solution. There was an immediate, copious evolution of water. At the end of 2 hr. the solution was cooled, washed with saturated aqueous sodium bicarbonate and finally water. The solvent was removed *in vacuo* to leave behind an oil which was crystallized from methanol to yield 7.62 g. (72%) of the indene, m.p. 54–62°. One further crystallization from the same solvent afforded 5.86 g. of yellowish granular crystals, m.p. 60–62°, resolidification, then 95–97°. A sample was further purified by recrystallization in methanol to yield IX, m.p. 61–62°, resolidification, then 97–97.5°.

Anal. Calcd. for $C_{22}H_{18}$: C, 93.57; H, 6.43. Found: C, 93.69; H, 6.39.

A sample of the olefin was dissolved in ether and seeded with the higher melting crystals. The m.p. of the crystals which remained when the solvent had evaporated (at room temp.) was 97–97.5°. The mixed m.p. of IX with VIII was 72–82°.

(b) **By Isomerization of the Indene VIII.**—One-half gram (0.0018 mole) of VIII was added to a well-stirred solution of 0.02 g. (0.0005 mole) of potassium in 25 ml. of *t*-butyl alcohol. The resulting amber solution was stirred overnight. The pink color which was produced when the reaction mixture was diluted with water (100 ml.) was dispelled with a few drops of hydrochloric acid. The gum which came out was taken up in ether and this solution washed with water. The ether was removed to leave behind a gummy residue that on crystallization from methanol afforded 123 mg. of solid, m.p. 80–95°. Two further recrystallizations from the same solvent yielded 75 mg. of granular yellow crystals, m.p. 94.5–97°; mixed m.p. with IX, 94–97°; mixed m.p. with VIII, 68–82°. Similar treatment of 1.0 g. of the indene IX led to the recovery of 0.52 g. of starting material, m.p. 92–95°; mixed m.p. with pure IX 93–96°.

Conversion of the Tetralone VI to VII.—One gram of VI was reduced and the resulting crude alcohol dehydrated in exactly the manner as that used in obtaining VIII to yield 0.73 g. (77%) of 1,2-dihydro-2,3-diphenylnaphthalene (VII), m.p. 116–118°. One further recrystallization from ethanol afforded glistening needles, m.p. 118.5–119.5°, lit.[9] 120°.

Cyclization Studies. (a) **In Liquid Hydrogen Fluoride.**—One gram of the appropriate acid was dissolved slowly in 50 ml. of well-stirred liquid hydrogen fluoride. When the reagent had evaporated, the residue was dissolved in ether and the solution washed with 5% aqueous potassium hydroxide followed by water. The residue which remained when the solvent was removed was dried in a vacuum oven. The infrared spectrum of this was then determined in chloroform solution. The crude cyclization product of the high melting acid was recrystallized from ethanol to yield 0.65 g. (69%) of the tetralone, m.p. 144–147°.

(b) ***Via* the Acid Chloride.**—A suspension of 1.06 g. (0.0033 mole) of the acid and 0.75 g. (0.0036 mole) of phosphorus pentachloride in 40 ml. of benzene was warmed on a steam-bath for 0.5 hr. Stannic chloride (0.92 g., 0.0035 mole) was then added and the solution warmed on the steam-bath overnight. This was then poured into dilute hydrochloric acid. The mixture was extracted with ether, and the extract washed with aqueous potassium hydroxide and water; the solvent was then evaporated. The infrared spectrum of the residue was determined as above. Crystallization of the crude product obtained from the high melting acid afforded 0.62 (63%) of the tetralone, m.p. 143–147°; the crude product of the low melting acid yielded 0.33 g. (34%) of the ketone, m.p. 143–147°.

(c) **Incomplete Cyclization.**—A sample (2.10 g.) of the low melting acid was treated with phosphorus pentachloride and then stannic chloride exactly as above. In this case, however, the reaction mixture was decomposed at the end of one hour. The product was then worked up in the usual manner. Acidification of the alkaline washes afforded 0.73 g. (29%) of recovered starting material, m.p. 136–140°. The neutral product (whose infrared spectrum showed the same ratio of indanone to tetralone as product of complete reaction) was recrystallized from ethanol to give 0.76 g. (39%) of the tetralone, m.p. 143–147°.

Cyclization of 3,4-Diphenylbutyric Acid.—One gram of the acid X[15] was added to 50 ml. of liquid hydrogen fluoride. The product was worked up in the same manner as that described for the other cyclizations in this medium to afford 0.61 g. of 3-phenyltetralone, m.p. 64–65°, lit.[15] 65–66°.

DURHAM, NORTH CAROLINA

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[14] W. v. Miller and Rohde, *Ber.*, **25**, 2096 (1892).

[15] Prepared by the procedure of F. S. Spring, *J. Chem. Soc.*, 1332 (1934).