[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Five- vs. Six-membered Ring Formation in Acid-catalyzed Cyclizations. II. 3,4-Diphenylvaleric Acid and 2,3-Diphenylglutaric Acid[1,2]

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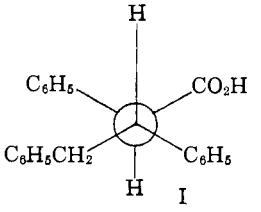
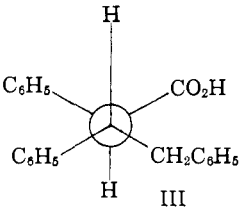
RECEIVED JULY 11, 1958

The configurations of the isomeric 3,4-diphenylvaleric acids have been determined by preparing these compounds from the corresponding butyric acids of known configuration. The *erythro*-acid (m.p. 132°) was found to give entirely a tetralone on cyclization, while the *threo*-acid (m.p. 100°) gave mainly the tetralone with traces of an indanone. The structures of the isomeric tetralones were proved by conversion to the substituted naphthalenes. The cyclization of *erythro*-2,3-diphenylglutaric acidalso gave mainly a tetralone, though in low yield.

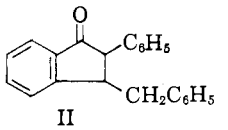
It has been demonstrated[2] previously that the cyclization of the diastereoisomeric 2,3,4-triphenylbutyric acids in liquid hydrogen fluoride leads to mixtures of the expected tetralone and the indanone. The ratio of the cyclization products was found to depend on the steric identity of the starting acid. Thus, the isomer I which was tentatively assigned the *erythro* configuration (and is shown below in the Newman projection[3] of the favored rotamer) led mainly to the indanone II. Similarly, the *threo*-acid III led to a mixture which was composed largely of the tetralone IV.



I



III



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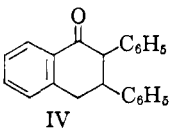
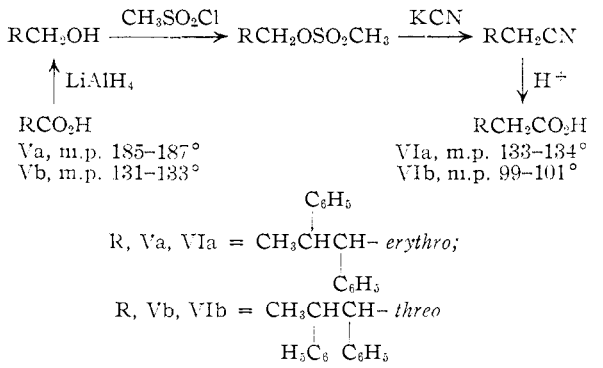


IV

The divergence in the path of these cyclizations was ascribed tentatively to the steric strain which would result when I assumed a conformation in which it could form a tetralone.

In the present investigation we wished to study the behavior on cyclization of acids whose configurations could be rigorously established and where the steric effects would be of a subtler nature.

Configuration and Cyclization of the Isomers of 3,4-Diphenylvaleric Acid.—Though both the isomers of VI have been known for some time,[4,5] their steric identity has not to date been determined. Since the configurations of the corresponding 2,3-diphenylbutyric acids have been established[6] (by conversion of the *erythro* isomer to the *meso*-diphenylbutane), it was decided to relate the valeric acid to the former. The homologation of each isomer of the butyric acid was conveniently achieved by reducing the acid, forming the methanesulfonate of the alcohol and effecting the displacement by cyanide in 66% aqueous dimethylformamide.[7] The scheme is outlined



This route proved very useful, not only for relating the configurations of the valeric acids to the butyric acids, but also for preparing the former acids in workable quantities, since none of the intermediates need be purified. Thus, in one run the acid VIb was obtained in an over-all yield of 84% starting with Vb. That the valeric acids VIa and VIb which were obtained were clearly different is taken as evidence for the fact that the stereochemical identity of the carbon skeleton remains unaffected by the above transformations.

The cyclization of the higher melting valeric acid (according to the present study, the *erythro* isomer) to a tetralone, melting at 68°, has been reported previously.[5] Since that work was carried out using hot sulfuric acid and it has been shown[2] that the direction of ring closure is dependent on the reaction conditions, the acid was cyclized with liquid hydrogen fluoride, which seems to favor the formation of indanones. The crude product exhibited an infrared absorption band at 5.95 μ with only a very slight shoulder at lower wave length, indicating that the tetralone is almost the sole product of the reaction.

Similar treatment of *threo*-3,4-diphenylvaleric acid afforded an oil which exhibited again a strong band at 5.95 μ. There was present, however, a sizeable shoulder at 5.82 μ which has been observed previously[2] with indanones. From the relative intensities of the two infrared absorption bands we estimated the indanone to be present to the extent of about 10%. Chromatography of the crude product on alumina afforded a 63% yield of a compound, m.p. 92.5–93.5°, which showed only the longer wave length carbonyl peak. An attempt to isolate the indanone was unsuccessful.

(1) Supported by the Office of Ordnance Research, U. S. Army.

(2) For the previous paper, see D. Lednicer and C. R. Hauser, THIS JOURNAL, **80**, 3409 (1958).

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

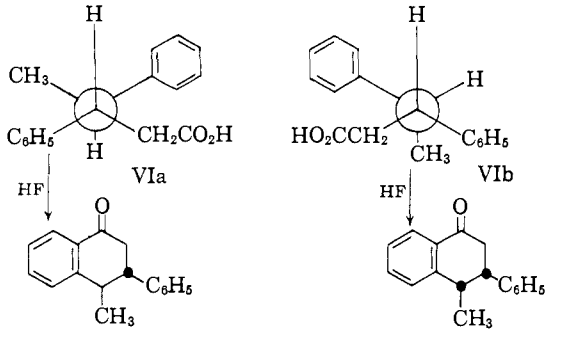
(4) H. Meerwein, *J. prakt. Chem.*, **97**, 264 (1918).

(5) F. S. Spring, *J. Chem. Soc.*, 1132 (1934).

(6) W. R. Brasen and C. R. Hauser, THIS JOURNAL, **79**, 395 (1957).

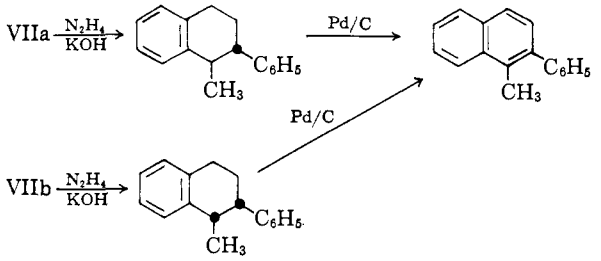
(7) See M. S. Newman and D. Lednicer, *ibid.*, **78**, 4765 (1956).

Cyclization of the *erythro* isomer of the acid VIa should lead to the *trans*-tetralone VIIa. By the same token, the *threo*-acid which does form the tetralone will lead to the *cis* isomer of the ketone.

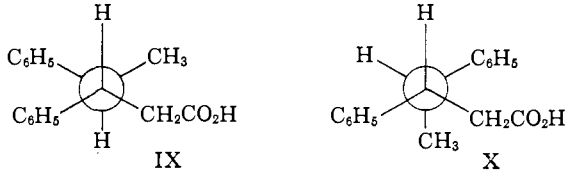


VIIa, m.p. 69–70.5° VIIb, m.p. 92.5–93.5°

Although it is established that the infrared absorption band at 5.95 μ is characteristic of a tetralone, it was thought desirable to provide chemical proof that the cyclization product, melting point 92.5–93.5°, is indeed the isomeric tetralone. This was accomplished by taking the ketone to the tetralin by means of a reduction and then aromatizing this compound. The product thus obtained proved identical to a sample of the known hydrocarbon prepared from the known[5] tetralone VIIa, melting point 68°.



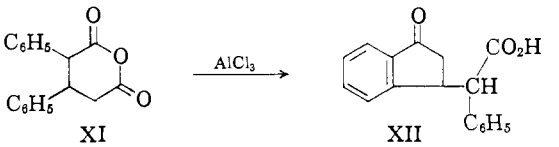
It would thus appear that the cyclization of each of the isomers of 3,4-diphenylvaleric acid produces predominantly the corresponding tetralone. Though infrared data suggest that a small proportion of the product from the *threo* isomer is an indanone, this could not be demonstrated by isolation.



While the projection formulas indicate that IX (which on ring closure would form an indanone) is the preferred rotamer of the acid, the conformation required to form a six-membered ring (X) is not a great deal more strained.[8] It is probable that the strain energy involved in X is not sufficient to outweigh the energy gained in forming a six- rather than a five-membered ring. The fact that some indanone is formed suggests that by suitably increasing the size of the group in the 4-position of the *threo* isomer of an analogous acid, the proportion of the indanone formed may also increase.

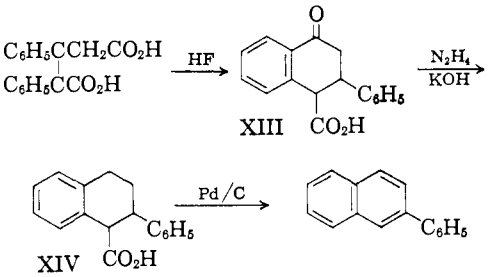
Configuration and Cyclization of 2,3-Diphenylglutaric Acids.—Both isomers of this acid are known, the one of melting point 208–210° being easily converted to that melting at 231–232°. On the basis of the optical rotations of the resolved acids, the former was assigned the *threo* configuration and the high melting isomer the *erythro* configuration.[9] In some earlier work[4] it was shown that the low melting glutaric acid and the low melting 3,4-diphenylvaleric acid (VIb) were configurationally related, since they are both obtainable from the m.p. 123° isomer of 3,4-diphenyl-Δ-valerolactone by oxidation and reduction, respectively. Since in the present investigation the low melting valeric acid was found to have the *threo* configuration, we have confirmed the earlier assignment of configurations to the glutaric acid.

It has further been demonstrated that cyclization of the anhydride XI of the glutaric acid, which has been shown by Avery and Maclay[9] and confirmed by us to have the *threo* configuration, affords a good yield of the indanone XII.[10] It



seemed possible that the cause for the formation of the indanone might again be steric. To avoid the additional complication of the direction of opening of the anhydride, the acids were used in this study.

Treatment of the higher melting *erythro*-acid with liquid hydrogen fluoride afforded a good (87%) yield of acidic material which exhibited absorption at both 5.82 and 5.95 μ. This material proved, however, to be grossly impure since repeated crystallization was necessary to obtain a 20% yield of a reasonably pure keto-acid. The pure product, melting at 152–154°, proved to be different from the indanone XII (melting point 153–155°) as shown by the strongly depressed melting point of an admixture of the two keto-acids. The fact that XII showed infrared absorption at 5.82 μ only while its pure isomer XIII



showed bands at both 5.82 and 5.95 μ suggested that the latter was a tetralone. Further support

(8) In the conformation IX there is one large–large group interaction and one medium–medium interaction, whereas in X the interactions are two large–medium and one medium–medium in addition to a "buttressing" effect. The relative importance of the various interactions is difficult to estimate qualitatively.

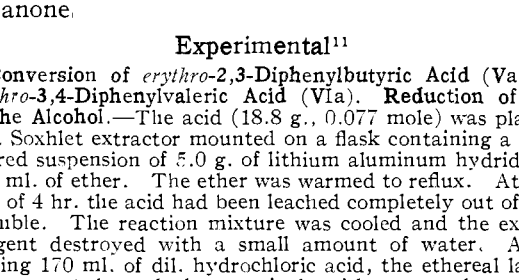
(9) S. Avery and W. D. Maclay, THIS JOURNAL, **51**, 2833 (1929).

(10) G. M. Badger, J. E. Campbell and J. W. Cook, *J. Chem. Soc.*, 1084 (1949).

for this view came from the observation that the product of the reduction of XIII showed only the 5.82 μ band. By way of final proof of the presence of the six-membered ring, the acid XIV was heated with palladium-on-charcoal to yield 2-phenylnaphthalene. It is of interest that decarboxylation and aromatization occurred simultaneously.

While the cyclization of the low melting *threo*-acid under the same conditions gave a good yield of acidic material, we were unable to isolate a pure compound from that product. Also, the composition of the product could not be estimated from the infrared spectrum, since absorption at 5.82 μ is common to the carbonyl group of both the acid and the indanone (see above).

Thus, while no conclusions can be drawn as to the stereochemistry of the ring closure of these two acids, it is worth noting that the *erythro* isomer is indeed the one which on steric grounds might be expected to form the six-membered ring. In the preferred conformation of that acid, the carboxyl



group is in a favorable position to form a tetralone. In contrast to this, the *threo*-acid, in the apparently preferred conformation, will tend to form an indanone.

Experimental[11]

Conversion of *erythro*-2,3-Diphenylbutyric Acid (Va) to *erythro*-3,4-Diphenylvaleric Acid (VIa). Reduction of Va to the Alcohol.—The acid (18.8 g., 0.077 mole) was placed in a Soxhlet extractor mounted on a flask containing a well stirred suspension of 5.0 g. of lithium aluminum hydride in 300 ml. of ether. The ether was warmed to reflux. At the end of 4 hr. the acid had been leached completely out of the thimble. The reaction mixture was cooled and the excess reagent destroyed with a small amount of water. After adding 170 ml. of dil. hydrochloric acid, the ethereal layer was separated, washed successively with saturated aqueous sodium bicarbonate and water, and finally dried over sodium sulfate. The solvent then was removed to leave behind 16.8 g. (95%) of the alcohol, m.p. 107–112°, lit.[6] 110–112°.

Conversion of the Alcohol to the Nitrile *via* the Methanesulfonate.—A solution of 16.8 g. (0.074 mole) of the alcohol obtained above in 80 ml. of pyridine was cooled in ice and treated with 10.0 g. of methanesulfonyl chloride. The mixture, from which solid soon separated, was allowed to come to room temperature. At the end of 3 hr. the mixture was diluted to 1 l. with water. The solid which formed on scratching was collected by filtration and recrystallized from high boiling (60–90°) petroleum ether to yield 17.8 g. (79%) of the methanesulfonate, m.p. 91–93°.

The ester then was added to a warm (60°) solution of 16.8 g. of potassium cyanide and 0.4 g. of potassium iodide in 130 ml. of DMF (dimethylformamide) and 70 ml. of water. The resulting solution now was warmed at 80–90° (stirring) for 2.5 hr. The solution then was poured onto 1 l. of ice-water and this suspension extracted with ether. The organic solution was washed with water and dried over sodium sulfate. Evaporation of the solvent afforded 12.2 g. of the crude nitrile. Two recrystallizations of the product from ethanol afforded 7.95 g. (62%) of small needle-like prisms, m.p. 82–85°. A small sample was recrystallized from the same solvent to a constant m.p. of 85–86°.

Anal. Calcd. for $C_{17}H_{17}N$: C, 86.77; H, 7.28; N, 5.95. Found: C, 86.91; H, 7.37; N, 5.94.

Hydrolysis of the Nitrile to VIa.—A solution of 1.0 g. (4.3 mmoles) of the nitrile in 10 ml. of acetic acid containing 1 ml. of 50% sulfuric acid was heated under reflux for 24 hr. When the clear solution was poured into water, a solid quickly separated. This was recrystallized from high boiling (60–90°) petroleum ether to yield 0.92 g. (85%) of the acid as fine powdery needles, m.p. 133.5–134.5°, lit.[5] 132°.

Conversion of *threo*-2,3-Diphenylbutyric Acid[12] to *threo*-3,4-Diphenylvaleric Acid.—The conversions carried out in this series were identical in detail to the analogous reactions employed in the *erythro* series. The alcohol, which was in this case an oil, was not purified. This alcohol was converted to the methanesulfonate, m.p. 78–79°.

Anal. Calcd. for $C_{17}H_{20}O_3S$: C, 67.08; H, 6.62. Found: C, 67.24; H, 6.84.

The nitrile was not purified since it too is a liquid. This oil was hydrolyzed as above to afford the acid, m.p. 99–100°, lit.[4] 109°.

Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 79.93, 80.09; H, 7.01, 7.11.

In one run 18.3 g. of the butyric acid was converted (without purification or crystallization of any of the intermediates) to 16.2 g. (84%) of the valeric acid, m.p. 96–98°.

Cyclization of *erythro*-3,4-Diphenylvaleric Acid.—To 30 ml. of liquid hydrogen fluoride was added 1.0 g. (4 mmoles) of the acid. The solid which remained when the liquid had evaporated was washed with water and dissolved in ether. This solution was then washed with saturated aqueous sodium bicarbonate and water. The solid which remained when the solvent was removed was crystallized from high boiling (60–90°) petroleum ether to yield 0.71 g. (76%) of the tetralone, m.p. 69–70.5°, lit.[5] 68°.

Reduction of Tetralone VIIa.—A suspension of 5.70 g. (2.4 mmoles) of the ketone and 4.3 g. of potassium hydroxide in 75 ml. of ethylene glycol and 22 ml. of hydrazine hydrate was heated under reflux for 30 min. Water was then allowed to distil over. When the temperature reached 150°, gas evolution was noted in the attached gasometer. The temperature was allowed to rise to 185°. At the end of 1 hr. the theoretical volume of nitrogen had been collected. The hot solution was poured onto ice-water and the resulting suspension extracted with ether. The organic solution was washed with water and dried over sodium sulfate. The oil which remained when the solvent was removed solidified on scratching to afford 4.72 g. (89%) of the hydrocarbon, m.p. 38–41°. Recrystallization from low boiling petroleum ether (cooling in deep freeze) afforded white crystals, m.p. 41–42°.

Anal. Calcd. for $C_{17}H_{18}$: C, 91.84; H, 8.16. Found: C, 92.03; H, 8.14.

Aromatization of *trans*-1-Methyl-2-phenyl-1,2,3,4-tetrahydronaphthalene.—An intimate mixture of 0.3 g. of the hydrocarbon and 0.2 g. of 10% palladium-on-charcoal was heated in a bath at 245–250° for 2 hr. The cooled melt was taken up in ether and the catalyst removed by filtration. The solid which remained on evaporation of the solvent was crystallized from ethanol to afford 0.26 g. (87%) of fine glistening plates, m.p. 80–83°. One further crystallization from the same solvent brought the m.p. to 84–85°, lit.[5] 84°.

Cyclization of *threo*-3,4-Diphenylvaleric Acid.—To 100 ml. of liquid hydrogen fluoride was added 5.0 g. of the *threo*-acid. The residue was worked up as above to afford a gummy oil. This product shows infrared bands at both 5.82 and 5.95 μ in a ratio suggesting that the indanone is present in a concentration of about 10%. The oil was then placed on an alumina column and eluted with 10% chloroform in low boiling (30–60°) petroleum ether. From the eluates (3 l.) there was obtained 3.36 g. of crystalline solid. This crude product was recrystallized from high boiling (60–90°) petroleum ether to yield 2.93 g. (64%) of the tetralone as colorless granules, m.p. 92–93.5°; concentration of the solvent afforded 0.35 g. (7%) of a second crop, m.p. 89–92°. One further crystallization of the main fraction from the same solvent afforded the analytical sample, m.p. 92.5–93.5°, λ_{max} 5.95 μ.

Anal. Calcd. for $C_{17}H_{16}O$: C, 86.40; H, 6.83. Found: C, 86.61; H, 6.97.

(11) All melting points are recorded as obtained on a Fisher–Johns block. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(12) C. R. Hauser, D. Lednicer and W. R. Brasen, THIS JOURNAL, **80**, 4345 (1958).

Reduction of the Tetralone VIIb.—The ketone (2.93 g.) was added to a mixture of 2.2 g. of potassium hydroxide, 11.5 ml. of hydrazine hydrate and 40 ml. of ethylene glycol. The reaction was carried out and the product obtained in the same manner as described above. After three recrystallizations from low boiling (30–60°) petroleum ether (chilling), there was obtained 1.85 g. (68%) of the crystalline hydrocarbon, m.p. 50–55°. A sample was recrystallized from the same solvent to a constant m.p. of 58–60°.

Anal. Calcd. for $C_{17}H_{18}$: C, 91.84; H, 8.16. Found: C, 91.82; H, 8.03.

Aromatization of *cis*-1-Methyl-2-phenyl-1,2,3,4-tetrahydronaphthalene.—A small sample (0.30 g.) of the hydrocarbon and 0.20 g. of catalyst was heated at 230° for 2 hr., and then at 250° for an additional hr. The reaction mixture was treated as above to yield 0.21 g. (70%) of flaky plates, m.p. 82–84.5°. This was again recrystallized to afford a sample, m.p. 84–85°. The mixed m.p. of this with the substituted naphthalene obtained from the *trans*-hydrocarbon was 84–85°.

Cyclization of *erythro*-2,3-Diphenylglutaric Acid.—To 100 ml. of liquid hydrogen fluoride there was added 5.0 g. (0.018 mole) of the glutaric acid.[13] The clear gum which remained when the liquid had evaporated was washed with water and taken up in ether. The ethereal solution was then extracted with aqueous sodium bicarbonate. The gum which came out on acidification of this solution was crystallized from aqueous ethanol to give 1.27 g. of crystalline solid, m.p. 135–145° (melting and resolidification 79°). Material of adequate purity for further work, m.p. 144–153°, was obtained by one further crystallization from the same solvent. A sample was recrystallized from ethyl acetate–high boiling (60–90°) petroleum ether to give tiny glistening plates, m.p. 152–154°, λ_{max} 5.82, 5.95 μ. The mixed m.p. of this with a sample of the indanone XII,[10] m.p. 152.5–155°, was 125–135°.

Anal. Calcd. for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: C, 76.91; H, 5.38.

Conversion of the Keto-acid XIII to the Acid XIV.—A solution of 0.97 g. (3.6 mmoles) of the keto-acid and 0.70 g. of potassium hydroxide in 14 ml. of ethylene glycol and 4 ml. of hydrazine hydrate was heated under reflux for 30 min. The temperature of the mixture was then raised to 192° by allowing water to distil over. The evolution of gas, which started at 150°, was complete after 45 min. The cooled solution then was diluted with water (100 ml.) and washed with ether. The solid which came out on acidification of the aqueous solution was collected by filtration and crystallized from aqueous ethanol to yield 0.70 g. (75%) of the acid, m.p. 142–145°. Repeated crystallization from the same solvent yielded a sample m.p. 144.5–146°, λ_{max} 5.83 μ.

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.74; H, 6.61.

Aromatization and Decarboxylation of Acid XIV.—An intimate mixture of 0.18 g. of the acid and 0.075 g. of 10% palladium-on-charcoal was placed in a bath at 160°. Over 10 min. the temperature was brought to 265°. After an additional 10 min. the mixture was allowed to cool. The solid was taken up in ether and the catalyst removed by filtration. The solid, m.p. 94–99° (0.15 g.), which remained when the ethereal solution was taken to dryness was crystallized from aqueous ethanol. There were obtained glistening colorless flakes of 2-phenylnaphthalene, m.p. 101.5–102.5°, lit.[14] 103–104°. The ultraviolet absorption spectrum of this compound is identical to that in the literature.[15]

Preparation of *threo*-2,3-Diphenylglutaric Acid from the Anhydride XI.—To a solution of 5.68 g. (0.02 mole) of the anhydride[10] in 25 ml. of acetone was added cautiously with stirring 20 ml. of 2 *N* sodium hydroxide at such a rate as to keep the solution just basic. When the reaction was complete the solution was diluted with 300 ml. of water and washed with ether. Acidification with dilute hydrochloric acid afforded a white solid which was collected by filtration. One crystallization from ethanolic water afforded 4.72 g. of the acid m.p. 205–210°, lit.[9] 208–210°.

Attempted Cyclization of *threo*-2,3-Diphenylglutaric Acid.—A sample of the acid (1.80 g.) was dissolved in 50 ml. of liquid hydrogen fluoride. This was worked up in the same manner as the mixture obtained from the cyclization of the isomeric acid. In this case, however, no pure crystalline material could be obtained.

(13) Obtained by fractional crystallization of a mixture containing *threo*- and *erythro*-acids prepared by the method of C. R. Hauser and M. T. Tetenbaum, *J. Org. Chem.*, **23**, 1146 (1958).

(14) W. Smith and T. Takamatsu, *J. Chem. Soc.*, **39**, 546 (1881).

(15) R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951, structure 297.

DURHAM, N. C.

[CONTRIBUTION FROM STANFORD RESEARCH INSTITUTE]

A Study of a Thioketo–Thioenol Tautomeric System. I. Ethyl Thiobenzoylacetate[1]

BY ZOILA REYES AND ROBERT M. SILVERSTEIN

RECEIVED JUNE 2, 1958

It was shown that the decolorization of a solution of ethyl thiobenzoylacetate by oxygen can be attributed to a rapid oxidation of the colored thione tautomer, and the return of the color upon removal of oxygen to the slower reestablishment of the equilibrium thione concentration. The equilibrium picture was inferred from infrared and nuclear magnetic resonance spectra, and from iodimetric titration. The effect of oxygen upon the equilibrium was followed spectrophotometrically and manometrically.

Ethyl thiobenzoylacetate ($C_6H_5CCH_2COOEt$, with S) was obtained as a deep blue distillate by treating ethyl benzoylacetate ($C_6H_5CCH_2COOEt$, with O) with hydrogen sulfide and hydrogen chloride, precipitating the sulfur compound as the lead salt, regenerating with hydrogen sulfide and distilling. In contact with air, the blue color of ethyl thiobenzoylacetate gradually disappeared. When the dissolved air was removed by evacuation, by boiling in a solvent or by flushing with nitrogen, the blue color reappeared. This cycle could be repeated a number of times, but eventually the decolorization would be irreversible.

Polymerization and depolymerization as have been reported for a number of thiones[2] were not the explanation since there was no apparent change in viscosity on decolorization. Furthermore, the infrared and the n.m.r. spectra of the blue material and of the material just decolorized with air were

(1) Presented in part at the 133rd Meeting of the American Chemical Society, San Francisco, Calif., April, 1958.

(2) For a general review of thione chemistry, see E. Campaigne, *Chem. Revs.*, **39**, 1 (1946); A. Schönberg and A. Wager, in "Methoden der Organischen Chemie," (Houben-Weyl), Georg Thieme Verlag, Stuttgart, 1955, p. 695. Thiobenzoylacetates have not been previously described.