clotting time (t_C), and diminish the opacity both compared at constant time (t) after addition of thrombin and at constant t/t_C. The exceptions, starch and polyvinyl alcohol, shorten the clotting time.

3. The effectiveness in prolonging clotting time (expressed by d log t_C/dc, where c is concentration) and in diminishing opacity (expressed by the value of c at which opacity at constant t/t_C is one-half the control value) is generally greatest for compounds with one or two hydroxyls and several methylene or methyl groups, although specific characteristics are apparent.

4. Three reagents—hexamethylene glycol, pentamethylene glycol, and bis-(2-hydroxyethyl)-sulfide—prevent clotting entirely at moderate concentrations but cause no apparent irreversible changes in either fibrinogen or thrombin.

5. The results are interpreted as due to van der Waals association of the reagents with fibrinogen, and consequent steric interference with both end-to-end and side-by-side union of fibrinogen molecules.

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[CONTRIBUTION FROM THE JOHN HARRISON LABORATORY OF THE UNIVERSITY OF PENNSYLVANIA]

Cyclization of α-Phenylglutaric Anhydride

BY E. C. HORNING AND A. F. FINELLI[1]

From an extensive study by Attwood, Stevenson and Thorpe[2] on the cyclization of dicarboxylic acids derived from γ-phenylbutyric acid, the generalization was drawn that substitution in the β-position (with respect to the ring) was necessary for cyclization. For example, both β-benzylglutaric acid and α-benzylsuccinic acid gave tetralones on treatment with sulfuric acid; it was postulated that anhydride formation occurred first, and that cyclization then followed under the influence of concentrated acid. The effect of a β-substituent was not clearly defined, but since every instance in which cyclization occurred included this structural feature, the generalization seemed valid.

In the course of work on the synthesis of certain substituted tetralones, we have investigated the cyclization of α-phenylglutaric anhydride. This compound was prepared from phenylacetonitrile by the following steps. Carbethoxylation of phenylacetonitrile with diethyl carbonate by a modification of the usual method[3] gave ethyl phenylcyanoacetate (I). Addition of acrylonitrile to the latter compound provided α-phenyl-α-carbethoxyglutaronitrile (II); this was hydrolyzed and decarboxylated to the corresponding glutaric acid, which was then converted to the anhydride with acetic anhydride. Treatment of α-phenylglutaric anhydride (III) with sulfuric acid gave 4-keto-1,2,3,4-tetrahydro-1-naphthoic acid (IV) in 57% yield.

It was recognized by the English workers that α-phenylglutaric acid or its anhydride should be investigated as a simple test case for their generalization, but unfortunately the method of Fichter and Merckens[4] for the preparation of the acid could not be repeated. Since the original work, instances in which this generalization does not hold have been found; for example, Robinson[5] has described the cyclization of 5-carboxy-4-carboxymethyl-7-phenylheptanoic acid with sulfuric acid to the corresponding tetralone. The present method provides a satisfactory way of obtaining α-phenylglutaric anhydride, and its successful cyclization confirms the view that substitution in the β-position with respect to the ring is not a prerequisite for cyclization. At the same time, the conditions of cyclization may determine the nature of the product. When the anhydride was treated with aluminum bromide in benzene, an intermolecular reaction occurred with formation of α-phenyl-γ-benzoylbutyric acid. It has recently been demonstrated[6] that benzene is a suitable solvent for intramolecular Friedel–Crafts reactions, and this result indicates that sulfuric acid may give results different from those obtained under Friedel–Crafts conditions.

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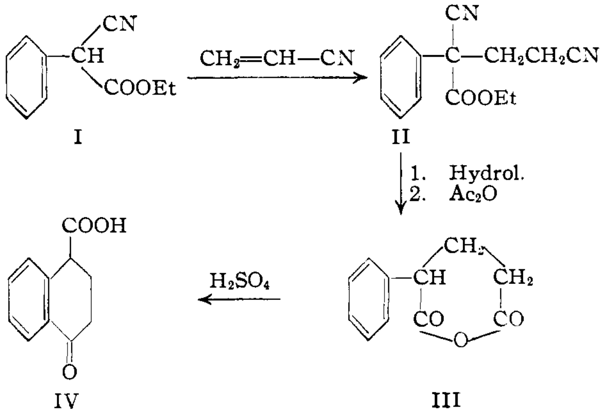

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[4] Fichter and Merckens, *Ber.*, **34**, 4174 (1901).

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Experimental

All melting points are corrected.

Ethyl Phenylcyanoacetate.—Sodium ethoxide was prepared from 12.0 g. (0.52 mole) of sodium and 300 ml. of anhydrous ethanol in a 1-l. three-necked, round-bottomed flask fitted with a reflux condenser and drying tube. After the sodium dissolved, the excess ethanol was removed by heating the flask on a steam-bath while the system was maintained at the pressure obtained with an ordinary aspirator.

As rapidly as possible, after removal of the ethanol, the flask was fitted with a stirrer, a dropping funnel, a distilling head with thermometer, and a condenser arranged for distillation into a flask protected by a calcium chloride tube. There was added 300 ml. of dry diethyl carbonate, 80 ml. of dry toluene, and 58.5 g. (0.50 mole) of phenylacetonitrile. The flask was heated with good stirring and when distillation started, dry toluene was added dropwise at about the same rate as that of distillation. Approximately 200–250 ml. of toluene was added over a period of two hours while stirring and distillation was continued.

The mixture was cooled, transferred to a beaker, and after addition of 300 ml. of cold water, the aqueous phase was acidified with 35–40 ml. of acetic acid. The layers were separated, and the water solution was extracted with three 75-ml. portions of ether. The organic solutions were washed with 100 ml. of water, and then dried over magnesium sulfate. The low-boiling solvents were removed by distillation at atmospheric pressure, and the residue was distilled under reduced pressure through a short (15 cm.) Vigreux column. After a 1–5 g. forerun, the product was collected as a colorless liquid at 125–135° (3–5 mm.). The yield was 66–74 g. (71–79%), $n^{25}\text{D}$ 1.5012–5019.

α-Phenyl-α-carbethoxyglutaronitrile.—A solution of 57.0 g. (0.30 mole) of ethyl phenylcyanoacetate in 80 ml. of *t*-butyl alcohol was heated to 40°, and with stirring the dropwise addition of a solution of 33.0 g. (0.62 mole) of acrylonitrile in 30 ml. of *t*-butyl alcohol was started. After the addition of about 10–15 drops, 1.0 ml. of 30% methanolic potassium hydroxide was added, and the temperature was maintained at 40–45° by occasional external cooling while the remaining solution was added slowly. When about one-half of the acrylonitrile was added an additional 1.0 ml. of potassium hydroxide solution was added. When the temperature was no longer maintained above 40° by the exothermic reaction, a hot-water-bath was employed to keep the mixture at 40–45° for one hour and it was then allowed to stand overnight.

The solution was diluted with 250 ml. of water, and acidified with 10% hydrochloric acid (30–40 ml.). The product was separated with 100 ml. of ether, and the aqueous solution extracted with two 50-ml. portions of ether. The combined extracts were washed with 50 ml. of water and dried over magnesium sulfate. The ether was distilled at atmospheric pressure, and the residue was distilled under reduced pressure through a short (15-cm.) Vigreux column. After a forerun of a few grams, the product was collected as a colorless viscous oil at 157–167° (0.5–1 mm.). The yield was 50–61 g. (69–83%), $n^{25}\text{D}$ 1.5100–5103.

Anal. Calcd. for $C_{14}H_{14}O_2N_2$: C, 69.40; H, 5.82. Found: C, 69.59; H, 6.04.

α-Phenylglutaric Anhydride.—A mixture of 48.4 g. (0.20 mole) of α-phenyl-α-carbethoxyglutaronitrile, 225 ml. of hydrochloric acid (sp. gr. 1.19) and 50 ml. of acetic acid was heated under reflux for ten hours. After cooling, the solution was diluted with 300 ml. of water. The α-phenylglutaric acid was extracted with five 100-ml. portions of ether–ethyl acetate (1:1). The extracts were combined and dried over magnesium sulfate. The solvents were removed as completely as possible by heating on a steam-bath, and the residue was transferred to a 200-ml. flask. Acetic anhydride (50 ml.) was added, and the solution was heated under gentle reflux for one hour. The excess acetic anhydride was removed by distillation at atmospheric pressure, and the residue was distilled under reduced pressure through a short (15 cm.) Vigreux column. The product was collected at 178–188° (0.5–1 mm.). The yield was 32.7 g. (86%); m. p. 90–94°.

This material was recrystallized from ethyl acetate–hexane to give a colorless crystalline product, m. p. 95–96°. The acid and its anhydride have been reported by Fichter and Merckens.[4]

α-Phenyl-γ-benzoylbutyric Acid.—To a solution of 14.4 g. (0.06 mole) of anhydrous aluminum bromide in 30 ml. of dry benzene there was added a solution of 3.8 g. (0.02 mole) of α-phenylglutaric anhydride dissolved (with warming) in 20 ml. of dry benzene. After the ensuing exothermic reaction the mixture was refluxed for twenty minutes and allowed to stand overnight.

The solution was decomposed with ice and concentrated hydrochloric acid. Approximately 30 ml. of ether was added to aid in the separation. The aqueous layer was extracted with three 30-ml. portions of ether. The combined organic extracts were washed with water. The organic layer was filtered and extracted with six 25-ml. portions of 10% sodium carbonate solution. The alkaline extract was filtered and acidified with hydrochloric acid (10%) to precipitate the organic acid. The mixture was chilled for two hours, filtered, and the product washed with cold water and dried at room temperature to yield 3.6 g. (67%) of crude colorless acid; m. p. 119–125°. Recrystallization from benzene–cyclohexane gave the acid as colorless needles, m. p. 130–131°.

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.00; H, 6.09.

4-Keto-1,2,3,4-tetrahydro-1-naphthoic Acid.—α-Phenylglutaric anhydride (4.0 g.) was dissolved with slight warming in 25 ml. of concentrated sulfuric acid, and the solution was kept at 60–70° for thirty minutes. This was allowed to stand overnight at room temperature. The solution was poured on chopped ice and allowed to stand until separation of the colorless solid product was complete. The crude material was removed by filtration and dried to yield 2.3 g. (57%); m. p. 91–92°. Recrystallization from ethyl acetate–pentane gave colorless needles, m. p. 93–95°.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30; neut. equiv., 190. Found: C, 69.57; H, 5.40; neut. equiv., 192.

The colorless **semicarbazone** melted at 237° (dec.).

Anal. Calcd. for $C_{12}H_{13}O_3N_3$: C, 58.29; H, 5.30. Found: C, 58.46; H, 5.20.

The orange **2,4-dinitrophenylhydrazone** was recrystallized from benzene; m. p. 255–256 (dec.).

Anal. Calcd. for $C_{17}H_{14}O_6N_4$: C, 55.13; H, 3.81. Found: C, 55.12; H, 3.68.

Summary

The preparation and cyclization of α-phenylglutaric anhydride to 4-keto-1,2,3,4-tetrahydro-1-naphthoic acid is described.

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