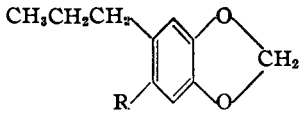
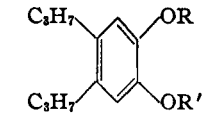
A Synthesis of β,β'-Dipropyladipic Acid

BY C. F. KOELSCH

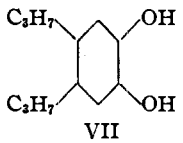
Part of the program referred to in the preceding note[1] was to establish the configuration of a synthetic homolog of hydroquinine by relating the substance to a 3,4-dipropylpiperidine. The synthesis of the latter compound and the determination of its configuration were to follow a route similar to the one used for 3,4-diethylpiperidine.[2] The program has been abandoned short of completion, but some of the reactions studied are of general interest and are being published. Those described in the present paper, indicated in the sequence of formulas (I–VIII), outline a synthesis of β,β'-dipropyladipic acid by a method which may prove of value for preparing other, similarly substituted, adipic acids.



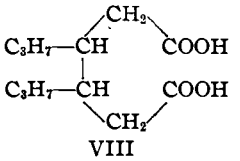
I, R = H
II, R = $COCH_2CH_3$
III, R = $CH_2CH_2CH_3$



IV, R + R' = CCl_2
V, R + R' = CO
VI, R = R' = H



VII



VIII

Experimental

Dihydrosafrole (I), b. p. 114° at 19 mm., was obtained in quantitative yield of shaking *iso*-safrole (400 g.) with Raney nickel and hydrogen at 100 atm. for five minutes. The hydrogenation was slightly exothermic, but it stopped when one equivalent of hydrogen had been taken up.

1,2-Methylenedioxy-4-propionyl-5-propylbenzene (II).—The action of propionic acid, propionic anhydride or propionyl chloride on dihydrosafrole alone or in the presence of sulfuric acid, zinc chloride, aluminum chloride or stannic chloride under varied conditions gave none or only traces of the desired compound. The procedure finally used was developed through many experiments, and its details must be rather carefully adhered to.

A mixture of 164 g. of dihydrosafrole, 100 g. of propionyl chloride, 50 ml. of phosphorus oxychloride and 100 ml. of toluene was boiled for fifty to fifty-five minutes, then poured into water and stirred until all of the acid chlorides were decomposed. The organic layer was washed with dilute sodium hydroxide and distilled at 26 mm., giving 92 g., b. p. 80–155°; 79 g., b. p. 155–205°; and 14 g. of residue. The lower fraction was mainly dihydrosafrole and could be used as such in a later propylation. Three hundred and six grams of the fraction b. p. 155–205°, from several acylations, was dissolved in 300 ml. of ligroin (30–60°) and cooled to −10°. The resulting crystals were pressed well and washed with cold ligroin, giving 160 g. of nearly pure II. A portion redistilled (b. p. 184–186° at 24 mm.) and recrystallized from ligroin, formed thick colorless plates, m. p. 51–52°.

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.9; H, 7.3. Found: C, 71.2; H, 7.3.

The oily chlorinated material remaining in the mother liquor, 124 g., b. p. 140–200° at 24 mm., was not investigated.

A mixture of 2.2 g. of II, 5 ml. of alcohol, 1.4 g. of butyl nitrite and 0.5 ml. of hydrochloric acid was allowed to stand for twenty-four hours, and then poured into ether and water. Dilute sodium hydroxide removed **1,2-methylenedioxy-4-(α-oximinopropionyl)-5-propylbenzene** (1.9 g.), pale yellow needles from ether–ligroin, m. p. 99–101°.

Anal. Calcd. for $C_{13}H_{15}NO_4$: C, 63.7; H, 6.1. Found: C, 63.2; H, 6.5.

When 0.7 g. of the oximino compound was stirred for fifteen minutes with a mixture of 5 ml. of hydrochloric acid, 5 ml. of acetic acid and 0.4 ml. of formalin, it yielded the corresponding diketone, a bright yellow oil. With excess hydrogen peroxide and alcoholic sodium hydroxide this gave ***o*-propylpiperonylic acid**, colorless flat needles (0.1 g.) from 30% acetic acid, m. p. 139–141°. The same acid was obtained directly from the oximino compound in poor yield with alkaline permanganate, and in 30% yield with hot acetic anhydride.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.5; H, 5.8. Found: C, 63.7; H, 5.8.

***o*-Propylpiperonylamide**, from the acid with thionyl chloride and then ammonia, formed fine white needles from benzene, m. p. 179°.

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.8; H, 6.3. Found: C, 63.7; H, 6.1.

1,2-Methylenedioxy-4,5-dipropylbenzene (III), a colorless almost odorless oil, b. p. 158–160° at 23 mm., m. p. 25°, was obtained in 75–80% yield by boiling 100 g. of II and 10 g. of resorcinol for eight hours with 240 g. of amalgamated zinc and 250 ml. of water, 750 ml. of hydrochloric acid being added in portions.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.7; H, 8.7. Found: C, 75.9; H, 8.8.

The methylenedioxy group in III was opened by the method of Fittig and Remsen.[3]

1,2-Dichloromethylenedioxy-4,5-dipropylbenzene (IV), colorless crystals that fume in moist air, b. p. 184–187° at 23 mm., m. p. 34–35°, was obtained in 79–84% yield by heating 88 g. of III with 190 g. of phosphorus pentachloride for one-half hour at 110–120°, and then for one hour at 150–160°. The reaction was carried out in a 500-ml. Claisen flask, phosphorus trichloride distilling as it was formed.

Anal. Calcd. for $C_{13}H_{16}Cl_2O_2$: Cl, 25.8. Found: Cl, 25.7.

4,5-Dipropylpyrocatechol carbonate (V), colorless plates from alcohol, m. p. 70–73°, was obtained in 99% yield when 93 g. of IV was stirred with 200 ml. of water for one hour while the mixture was cooled so that its temperature remained at 55–60°.

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.9; H, 7.3. Found: C, 71.3; H, 7.3.

4,5-Dipropylpyrocatechol (VI).—A suspension of 73 g. of V in 75 ml. of alcohol was treated with 30 g. of sodium hydroxide in 200 ml. of oxygen-free water, boiled for thirty minutes under nitrogen, and then acidified with acetic acid. The product was separated using ether, washed with dilute sodium carbonate, and then distilled, giving 49 g. (76%), b. p. 184–187° at 15 mm. The substance crystallized when it was cooled, but it was too soluble to be recrystallized; m. p. *ca.* 43°. Its alkaline solution rapidly became green-blue, then brown when it was exposed to air. With ferric chloride, the phenol gave a deep green color, changing to purple with sodium hydroxide. It caused only slight erythema when applied to the skin.

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.2; H, 9.3. Found: C, 74.0; H, 9.0.

The **lead salt** formed as a white gelatinous precipitate that dried to a horny mass, when a solution of VI in methanol was treated with lead acetate. Two different preparations were analyzed.

(1) Koelsch, THIS JOURNAL, **68**, 146 (1946).

(2) Koelsch and Stratton, *ibid.*, **66**, 1881 (1944).

(3) Fittig and Remsen, *Ann.*, **159**, 148 (1871); *cf.* Pauly, *Ber.*, **40**, 3096, 3488 (1907); Barger, *J. Chem. Soc.*, **93**, 563, 2085 (1908); Delange, *Bull. soc. chim.*, [4] **3**, 509 (1908).

Anal. Calcd. for $C_{12}H_{16}O_2Pb$: Pb, 51.8. Found: Pb, 50.8, 53.2.

When 3.4 g. of VI in 5 ml. of acetic acid was treated with 9 g. of bromine in 10 ml. of acetic acid, it was converted into **3,6-dibromo-4,5-dipropyl-*o*-quinone**, deep red prisms (4.2 g.) from acetic acid, m. p. 144–146°.

Anal. Calcd. for $C_{12}H_{14}Br_2O_2$: C, 41.1; H, 4.0. Found: C, 41.0; H, 4.2.

The quinone gave no pure product when it was treated with aqueous sodium hydroxide or with alkaline hydrogen peroxide. When it was warmed with zinc dust in acetic acid, it was rapidly and quantitatively reduced to **3,6-dibromo-4,5-dipropylpyrocatechol**, fine white needles from acetic acid, m. p. 83–84°.

Anal. Calcd. for $C_{12}H_{16}Br_2O_2$: C, 40.9; H, 4.6. Found: C, 41.0; H, 4.9.

4,5-Dipropylcyclohexanediol-1,2 (VII).—Experiments on the hydrogenation of VI with Raney nickel and hydrogen at 200 atm. and 175° were carried out before the promoting effect of alkali on similar reactions had been discovered,[4] and the results were erratic. Even in the best experiment, involving 43 g. of VI with freshly prepared catalyst, hydrogen absorption stopped after five hours, and there was obtained a mixture (43 g.) of VI and VII, b. p. 170–183° at 14 mm. Nothing was extracted from this mixture by aqueous alkali, and it was completely extracted from ligroin by Claisen alkali. Separation of 25 g. of the mixture was effected by treatment with alcoholic lead acetate, which precipitated the VI as its lead salt, removed by centrifuging. There was obtained 13 g. of VII, a colorless viscous oil, b. p. 170–173° at 13 mm.

Anal. Calcd. for $C_{12}H_{24}O_2$: C, 72.0; H, 12.0. Found: C, 71.9; H, 11.7.

β,β′-Dipropyladipic Acid (VIII).—A solution of 6.2 g. of VII in 20 ml. of acetic acid was kept at 25–30° by cooling while 6.4 g. of chromic anhydride in 5 ml. of water and 15 ml. of acetic acid was added in small portions. The mixture was allowed to stand at room temperature for eight hours, and then distilled to a sirup under reduced pressure. This was taken up in ether, washed with dilute sulfuric acid and then with sodium carbonate, giving 1.35 g. of neutral material and 3.45 g. of crude acidic product. Crystallization of the latter from ligroin gave 3.3 g., m. p. 86–91°, and distillation of this at 15 mm. followed by crystallization from dilute acetic acid gave 2.65 g. of VIII, colorless needles, m. p. 94–95°.

Anal. Calcd. for $C_{12}H_{22}O_4$: C, 62.6; H, 9.5. Found: C, 62.3; H, 9.7.

No attempt to resolve VIII was made, but it may be noted that the formation of a *cis*-form of VII (and therefore a *meso*-form of VIII) is not certain because of the drastic conditions used for hydrogenating VI.

The author thanks Dr. S. T. Rolfson for most of the analyses reported in this paper.

(4) Ungnade and McLaren, THIS JOURNAL, **66**, 118 (1944); Ungnade and Nightingale, *ibid.*, **66**, 1218 (1944).

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A New Synthesis of 7,8-Diaminoquinoline

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Although 7,8-diaminoquinoline has been prepared previously[1] by coupling diazotized aniline with 7-aminoquinoline and reduction of the resulting azo-dye, we found it advisable to look for another procedure when large amounts of the diamine were needed. The following process was developed and it has been found to give satisfactory results.

When 7-nitroquinoline, obtained in a Skraup reaction from *m*-nitroaniline, was reduced by iron and 50% acetic acid, it gave an almost quantitative yield of 7-aminoquinoline. The latter was treated with toluenesulfonyl chloride in pyridine solution and the tosyl compound was nitrated below 70°. A nearly theoretical yield of the crude 7-tosylamino-8-nitroquinoline was obtained, and this was hydrolyzed by means of warm sulfuric acid. The resulting nitroamine was then reduced in the usual way with stannous chloride and hydrochloric acid. The yield of diaminoquinoline was 64% of the theoretical.

Experimental

7-Nitroquinoline.—Knueppel's procedure[2] was used. The compound melted without recrystallization at 128–130° (lit.[2] 130°); yield 14% (lit.[3] 6%).

7-Aminoquinoline.—One hundred and twenty-nine grams of 7-nitroquinoline was dissolved in 645 cc. of glacial acetic acid and 645 cc. of water was added while the solution was warmed to 60°. Maintaining the temperature at 60–70°, 103 g. of powdered iron was added in small portions to the well-stirred reaction mixture. When the reduction was complete, the mixture was cooled to room temperature and made alkaline by adding solid sodium carbonate in small portions with external cooling and stirring. After some standing, the precipitate was filtered, washed with water, and dried over calcium chloride in a desiccator. The dried powdered precipitate was extracted by refluxing with two liters of ether for two hours and repeating this process three times with fresh portions of solvent. The combined ether extracts were then dried with sodium sulfate and evaporated to dryness. Eighty-eight grams of fairly pure 7-aminoquinoline was obtained; m. p. 91–93° (lit.[4] 93.5–94°).

7-Tosylaminoquinoline.—Thirty-five grams of 7-aminoquinoline was dissolved in 250 cc. of dry pyridine and to the cold solution 45 g. of *p*-toluene-sulfonyl chloride was slowly added. The reaction mixture was heated for thirty minutes in a boiling water-bath under a reflux condenser, then cooled and poured into two liters of water. The precipitate was allowed to settle at 0°, filtered, washed with water and dried over calcium chloride; yield 47.5 g. The compound crystallized from ethyl alcohol in colorless prisms; m. p. 184–185°.

Anal. Calcd. for $C_{16}H_{14}N_2O_2S$: C, 64.43; H, 4.70. Found: C, 64.57; H, 4.72.

7-Tosylamino-8-nitroquinoline.—Seventeen grams of 7-tosylaminoquinoline was stirred slowly into 51 g. of concentrated nitric acid and the solution was maintained at 60–70° for two hours. After cooling, the solution was poured over 340 g. of ice. The mixture was kept in the refrigerator overnight, and the precipitated nitro compound was then filtered, washed with water, and dried in a desiccator; yield 24 g. The product was recrystallized, first from ethanol and then from 65% methyl alcohol. It formed colorless needles, m. p. 180°.

Anal. Calcd. for $C_{16}H_{13}N_3O_4S$: C, 55.98; H, 3.79. Found: C, 55.93; H, 3.95.

7-Amino-8-nitroquinoline.—Twenty-four grams of crude 7-tosylamino-8-nitroquinoline was stirred in small portions into 120 cc. of concentrated sulfuric acid. The solution was heated for one hour in a boiling water-bath, cooled to room temperature, and poured onto 700 g. of ice. An excess of ammonium hydroxide was added with stirring and

(1) Renshaw, Friedman and Gajewski, THIS JOURNAL, **61**, 3322 (1939).

(2) Knueppel, *Ber.*, **29**, 706 (1896).

(3) Kochanska and Bobranski, *ibid.*, **69**, 1807 (1936).

(4) Hamer, *J. Chem. Soc.*, 1436 (1921).