Synthesis of the *s*-Triazine System. V.[1] Cotrimerization of Imidates

FRED C. SCHAEFER

Central Research Division, American Cyanamid Co., Stamford, Connecticut

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Extension of the acid-catalyzed imidate trimerization reaction[2] to the cotrimerization case has been examined as a method for the preparation of unsymmetrically substituted *s*-triazines. Although the formation of mixtures is unavoidable, the process is convenient and affords a number of hitherto unavailable compounds.

It was to be expected that two imidates having approximately the same trimerization rates would co-react to give an essentially statistical distribution of all possible *s*-triazines. It was, in fact, found that a 2:1 mixture of ethyl acetimidate and propionimidate gave 2-ethyl-4,6-dimethyl-*s*-triazine and 2,4-diethyl-6-methyl-*s*-triazine in a combined yield of 52%. These two products were obtained in a molar ratio of 1.6:1. When the reactants were used in inverse ratio, the product ratio was almost precisely reversed.

If the two imidates trimerize at substantially different rates, the more reactive one tends to trimerize independently until its concentration is reduced to a relatively small value. Some cotrimers are then formed, and finally the residual sluggish reactant trimerizes slowly. Examples of this behavior were found in the cotrimerization of ethyl acetimidate with ethyl 2-chloropropionimidate and ethyl propionimidate with methyl benzimidate. In such cases, some improvement can be achieved by slow addition of the more reactive imidate to a mixture of the sluggish reagent and the catalyst.

Experimental[3]

Cotrimerization of Ethyl Acetimidate with Ethyl Propionimidate.—A mixture of ethyl acetimidate[2] (0.50 mole), ethyl propionimidate[2] (0.25 mole), and acetic acid (0.053 mole) was held at 30–35° for 18 hr. The solution was distilled, and the fraction boiling above 150° was diluted with ether, washed with aqueous carbonate, dried, and redistilled. The product mixture was analyzed by mass spectrometry. The yields, based on the limiting reagent, were as follows: 2-ethyl-4,6-dimethyl-*s*-triazine, 32%; 2,4-diethyl-6-methyl-*s*-triazine, 38%; 2,4,6-trimethyl-*s*-triazine[2] > 28%; 2,4,6-triethyl-*s*-triazine[2] 17%.

Several similar products were combined and fractionated to obtain the pure cotrimers: 2-Ethyl-4,6-dimethyl-*s*-triazine: b.p. 87° (43 mm.), $n^{25}D$ 1.4687.

Anal. Calcd. for $C_7H_{11}N_3$: C, 61.29; H, 8.08; N, 30.63. Found: C, 61.34; H, 8.22; N, 30.57.

2,4-Diethyl-6-methyl-*s*-triazine: b.p. 94° (6 mm.), $n^{25}D$ 1.4680.

Anal. Calcd. for $C_8H_{13}N_3$: C, 63.54; H, 8.66; N, 27.79. Found: C, 63.67; H, 8.93; N, 27.59.

Cotrimerization of Ethyl Acetimidate and Ethyl 2-Chloropropionimidate.—Ethyl 2-chloropropionimidate[4] (0.14 mole) and acetic acid (0.017 mole) were heated at 70° while ethyl acetimidate (0.29 mole) was added dropwise during 135 min. The reaction temperature was maintained for 16 hr. longer, after which the concentration of the residual imidate was low as judged by infrared spectroscopy. The products were distilled directly from the reaction mixture. Fractions were analyzed by gas-liquid chromatography using a silicone stationary phase and yields were calculated as given below. Boiling points and analytical data were determined on material fractionated from combined lots:

2-(1-Chloroethyl)-4,6-dimethyl-*s*-triazine.—37% yield, b.p. 99–102° (24 mm.), $n^{28.5}D$ 1.4901.

Anal. Calcd. for $C_7H_{10}N_3Cl$: C, 48.98; H, 5.87; N, 24.48; Cl, 20.66. Found: C, 49.23; H, 5.88; N, 24.64; Cl, 20.54.

2,4-Bis(1-chloroethyl)-6-methyl-*s*-triazine.—25% yield, b.p. 130–135° (24 mm.), $n^{27.5}D$ 1.5046.

Anal. Calcd. for $C_8H_{11}N_3Cl_2$: C, 43.65; H, 5.04; N, 19.09. Found: C, 43.60; H, 5.13; N, 19.03.

Cotrimerization of Ethyl Propionimidate with Methyl Benzimidate.—A mixture of ethyl propionimidate (0.25 mole), methyl benzimidate[5] (0.50 mole), and acetic acid (0.15 mole) was held at room temperature for 2 days. 2,4,6-Triphenyl-*s*-triazine[2] was then filtered from the mixture (32% yield, m.p. 225–230°), and the filtrate was diluted with water and ether. After neutralization with carbonate, the ether phase was separated and dried. Distillation gave methyl benzimidate (37% recovery) and 2,4-diethyl-6-phenyl-*s*-triazine, b.p. 125–130° (3 mm.), $n^{24}D$ 1.5595, in 31% yield based on the propionimidate used.

Anal. Calcd. for $C_{13}H_{15}N_3$: C, 73.21; H, 7.09; N, 19.70. Found: C, 73.00; H, 7.34; N, 19.49.

Recrystallization of the distillation residue from ethanol gave a 3% yield of 2-ethyl-4,6-diphenyl-*s*-triazine, m.p. 68–69°.[6]

(1) Paper IV, F. C. Schaefer and G. A. Peters, *J. Org. Chem.*, **26**, 2784 (1961).

(2) F. C. Schaefer and G. A. Peters, *ibid.*, **26**, 2778 (1961).

(3) Microanalysis were carried out in these laboratories under the direction of Dr. J. A. Kuck. Mass spectrometric analyses were obtained by Mr. A. H. Struck and Miss R. Herberich.

(4) F. C. Schaefer and G. A. Peters, *J. Org. Chem.*, **26**, 412 (1961).

(5) H. L. Wheeler, *Am. Chem. Soc. J.*, **17**, 398 (1895).

(6) H. Reinhardt and E. Schiefer, *Chem. Ber.*, **90**, 2643 (1957), give m.p. 66–67°.

Preparation of *ortho*-Alkyl- and *ortho*-Aralkylbenzoic Acids by Catalytic Hydrogenation of *ortho*-Acylbenzoic Acids

J. KOLLONITSCH, HOLLY E. MERTEL, AND VINCENT F. VERDI

Merck Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc., Rahway, New Jersey

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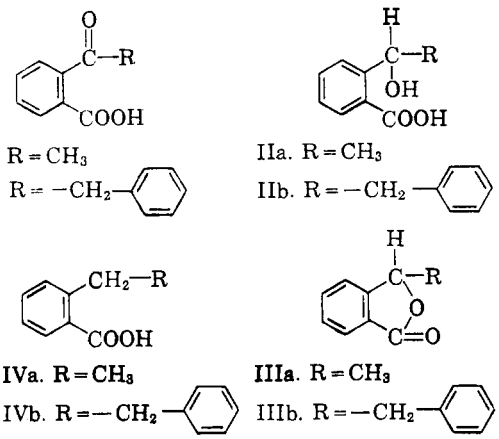
Reports of unsuccessful attempts to reduce *ortho*-acyl substituted benzoic acids into the corresponding alkyl- or aralkylbenzoic acids[1,2] (trying to utilize the Clemmensen method and catalytic hydrogenation, respectively) prompt us to disclose our positive results.

(1) R. Huisgen and E. Rauenbusch, *Ann.*, **641**, 51 (1961).

(2) Treibs and Klinkhammer, *Ber.*, **83**, 367 (1950); *ibid.*, **84**, 671 (1951).



Huisgen and Rauenbusch[1] reported that the catalytic reduction of Ia does not proceed beyond the hydroxy stage (IIa) which then cyclizes into the lactone (IIIa), which is not easily amenable to further reduction. We found that the desired reduction can be easily accomplished by working in neutral or slightly alkaline medium, this means in fact the reduction of a salt of Ia instead of Ia itself. The formation of the lactone (IIIa) is thus prevented. When Ia in the form of its sodium salt in water is hydrogenated with palladium on charcoal catalyst at 80° and a pressure of 40 p.s.i. two moles of hydrogen are absorbed in eight hours to afford IVa. The results are similar with 2-phenylacetylbenzoic acid (Ib). The hydroxy acid (IIb) can be also reduced into IVb under analogous conditions. The yields are in the range of 83–92%.

Experimental

2-Ethylbenzoic Acid (IVa).—A 16.4-g. sample of *o*-acetylbenzoic acid (Ia; 0.100 mole; from Aldrich Chemical Co.) was dissolved in a mixture of 100 ml. of 1.0 *N* sodium hydroxide solution and 70 ml. of water (pH 7). It was hydrogenated after the addition of 10 g. of Pd–Darco catalyst (10% palladium) at 40 p.s.i. starting pressure. After the uptake of 0.1 mole of hydrogen in 2 hr. further uptake ceased, therefore it was heated to 80° and hydrogenated for 6 hr. at 40 p.s.i. until another 0.1 mole of hydrogen was consumed. After filtration through Supercel and acidifying with hydrochloric acid 12.4 g. of IVa was obtained (83% yield) m.p. 62–63° (lit.,[1] m.p. 60–62°).

Anal. Calcd. for $C_9H_{10}O_2$: C, 71.9; H, 6.75. Found: C, 72.02; H, 6.95. Equiv. wt. (by titration) 149; theory 150.08.

2-Phenylethylbenzoic Acid (IVb). A. From 2-Phenylacetylbenzoic Acid (Ib).—A 22.2-g. sample of 3-benzalphthalide (0.100 mole) was transformed into the sodium salt of 2-phenylacetylbenzoic acid by saponification with a solution of 5 g. of sodium hydroxide in 100 ml. of water (20 min. at 90–95°). Fifty milliliters of water was added and the pH of the solution adjusted to 8.5 by the addition of hydrochloric acid. After cooling to room temperature the solution was filtered to remove a small amount of by-product; it was then hydrogenated after the addition of 7 g. of Pd–Darco catalyst (10% palladium) at 80° with a starting pressure of 40 p.s.i. In 8 hr. 0.2 mole of hydrogen was taken up and the uptake practically ceased. Acidification of the filtered solution gave 20.71 g. of IVb, m.p. 128–130° (lit., 130–131°; mixed m.p., the same; over-all yield 91.6%.

B. From 2-(1-Hydroxy-2-phenylethyl)benzoic Acid (IIb).—A solution of the sodium salt of 2-(1-hydroxy-2-phenylethyl)benzoic acid was prepared by saponifying 22.4 g. (0.100 mole) of 3-benzylphthlide[3] by refluxing for a short time with 5 g. of sodium hydroxide in 150 ml. of water. The solution of IIb then obtained was buffered to pH 8–9 by the addition of 14.2 g. of disodium phosphate and 1.1 ml. of 85% phosphoric acid. It was hydrogenated for 8 hr. at 120° at 40 p.s.i. with 3.5 g. Pd–Darco catalyst (5% palladiun). By acidification of the filtrate 19.7 g. of 2-phenylethylbenzoic acid was obtained (85% of theory); m.p. 125–128°; did not depress the melting point of an authentic sample of IVb.

(3) S. Natilson and S. P. Gottfried, *J. Am. Chem. Soc.*, **58**, 1432 (1936).

A Reinvestigation of the Hydrogenolysis of Hydroxyl Groups of the Stereoisomeric 3-Phenylcholestanols

EDGAR W. GARBISCH, JR.[1]

School of Chemistry, University of Minnesota, Minneapolis, Minnesota

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Recently Zderic, Rivera, and Limón found that Raney nickel hydrogenolysis of the hydroxyl groups of the epimeric 3-phenylcholestanols led to the common product, 3β-phenylcholestane.[2] Reportedly, the Raney nickel hydrogenolysis of 3α-phenylcholestan-3β-ol was the first instance in which a hydroxyl group was reduced with inversion of configuration.[3] A mechanism was proposed.[2]

Observations from work now underway have led to a reinvestigation of the hydrogenolysis of the 3-phenylcholestanol system.[2] The series of experiments summarized below demonstrate that W-2 Raney nickel hydrogenolysis of the hydroxyl groups of the stereoisomeric 3-phenylcholestanols indeed proceeded with a high degree of retention of configuration (probably > 90%), and that 3α-phenylcholestane was rapidly equilibrated to the thermodynamically more stable 3β-phenylcholestane by Raney nickel in refluxing ethanol.

In accordance with earlier reports,[2] the treatment of 3α-phenylcholestan-3β-ol (I) with Raney nickel in refluxing ethanol led to 3β-phenylcholestane (IV). Likewise, the hydroxyl group of 3β-phenylcholestan-3α-ol (II) was hydrogenolyzed to give pure IV.[4] The proton magnetic resonance spectrum of IV exhibits absorptions at 7.58τ and 2.89τ for the C-3 proton and phenyl protons, re-

(1) N. S. F. Postdoctoral Fellow, 1961–1962. Present address: Department of Chemistry, University of Chicago, Chicago 37, Illinois.

(2) J. A. Zderic, Ma. E. C. Rivera, and D. C. Limón, *J. Am. Chem. Soc.*, **82**, 6373 (1960).

(3) See Ref. 1 for background references. See also: D. Cram and J. Allinger, *ibid.*, **76**, 4516 (1954); D. Curtin and S. Schmukler, *ibid.*, **77**, 1105 (1955); and S. Mitsui and S. Imaizumi, *Bull. Chem. Soc. Japan*, **34**, 774 (1961).

(4) As little as 5% of III in IV or vice versa could be detected reliably in the infrared using the absorptions between 13.1 μ and 14.3 μ.