NOTES

1,2,3,4-Tetrahydro-2-methoxynaphthalene

By Harry A. Arbit

The hydrogenation of 2-methoxynaphthalene to "*ac*-tetrahydro-β-naphthyl methyl ether" over Raney nickel in 71 to 73% has been described by Adkins and co-workers.[1] However, no physical properties of this compound other than a boiling point of 115–118° at 10 mm. pressure are given and no reason is presented for the statement that hydrogenation had taken place in the oxygenated ring.

We have carried out the hydrogenation[2] of 2-methoxynaphthalene as described by Musser and Adkins.[1] The product (58% yield) was a water-white liquid with a sweet odor, b. p. 113–115° (9 mm.), $n^{25}D$ 1.5293. In order to obtain clear evidence that the methoxyl group was on the reduced rather than on the aromatic ring, the following experiment was carried out. Two grams of the liquid was refluxed for ten minutes with 10 ml. of hydriodic acid (sp. gr. 1.7). Methyl iodide was evolved and the product obtained (b. p. 120° (10 mm.), $n^{25}D$ 1.5635) was insoluble in 10% sodium hydroxide and gave a positive qualitative test for iodine after sodium fusion. It was therefore 1,2,3,4-tetrahydro-2-iodonaphthalene, formed by action of the hydriodic acid on the secondary alcohol, *ac*-tetrahydro-β-naphthol, after demethylation of the original compound. This same iodide was obtained when a known sample of *ac*-tetrahydro-β-naphthol[3,4] was similarly treated with hydriodic acid.

The compound formed by the hydrogenation of 2-methoxynaphthalene is thus shown to be 1,2,3,4-tetrahydro-2-methoxynaphthalene. The latter has been obtained by v. Braun and Weissbach[5] by the hydrogenation of 3,4-dihydro-2-methoxynaphthalene. These authors give the boiling point of the compound as 123–124° (16 mm.), and mention its pleasant odor.

(1) Van Duzee and Adkins, This Journal, **57**, 147 (1935); Musser and Adkins, *ibid.*, **60**, 664 (1938).

(2) The hydrogenation was carried out by Mr. W. M. Selby.

(3) Bamberger, *Ber.*, **23**, 197 (1890).

(4) Brochet and Cornubert, *Bull. soc. chim.*, [4] **31**, 1280 (1922).

(5) v. Braun and Weissbach, *Ber.*, **63**, 3052 (1930).

G. D. Searle and Co.
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Received May 9, 1946

A Simple Route to 2,3-Diphenyl-1,4-naphthoquinone

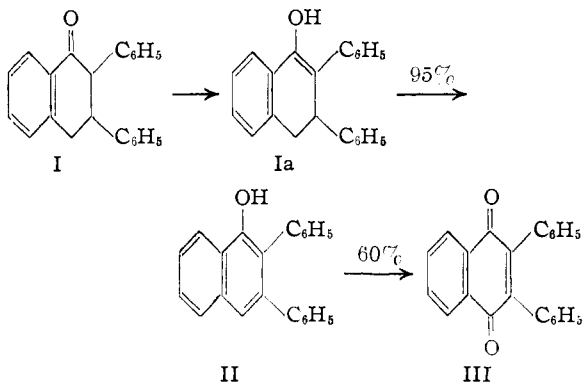
By Felix Bergmann and Jacob Szmuszkovic

Crawford and Nelson[1] recently described an improved method for the conversion of 2,3-diphenyl-1-keto-1,2,3,4-tetrahydronaphthalene (I) into 2,3-diphenyl-1,4-naphthoquinone (III) in an over-all yield of 30%, using a four-step process. During our studies on polyphenylnaphthalenes[2] we observed that the ketone I shows a pronounced tendency to enolize to Ia. It seemed, therefore, possible that its direct dehydrogenation would lead to 2,3-diphenyl-1-naphthol (II). This is indeed the case. Heating of I with one equivalent of sulfur at 250–300° gives a nearly quantitative yield of the naphthol (II), which can be oxidized to the quinone (III) in about 60% yield.

(1) Crawford and Nelson, This Journal, **68**, 134 (1946).

(2) F. Bergmann, Schapiro and Eschinazi, *ibid.*, **64**, 559 (1942).

Direct dehydrogenation of cyclic ketones to phenols has first been described by Darzens and Lévy.[3] The method was applied in a number of cases, using either sulfur or selenium,[4] but the yields are usually low. It is thus apparent that the enhanced enolizability of our ketone (I) has a favorable effect on the dehydrogenation to the corresponding naphthol (II), and one may presume that in every case the process consists essentially in the aromatization of an intermediate dihydronaphthalene derivative (such as Ia).



In this connection, it is of interest that catalytic dehydrogenation of cyclic ketones by means of palladium has been reported to give satisfactory yields (60–75%) of the corresponding phenols, especially if carried out in a solvent by prolonged heating.[5]

Experimental

2,3-Diphenyl-1-naphthol (II).—2,3-Diphenyl-1-keto-1,2,3,4-tetrahydronaphthalene (4.5 g.) and sulfur (530 mg.) were heated in a Pyrex tube. Reaction started at 250°, and this temperature was maintained for ten minutes and then raised slowly to 300° during thirty minutes. The black mass was distilled in a tube at 175–240° (0.6 mm.). The brown oil so obtained solidifies immediately; upon trituration with acetic acid, the substances showed a m. p. of 123–124°; yield, 4.3 g. The substance crystallized from acetic acid or petroleum ether (130°) in colorless plates, of m. p. 127–128°.[6]

Anal. Calcd. for $C_{22}H_{16}O$: C, 89.1; H, 5.4. Found: C, 88.9; H, 5.4.

(3) Darzens and Lévy, *Compt. rend.*, **194**, 181 (1932).

(4) (a) Cook and Hewett, *J. Chem. Soc.*, 403 (1933); (b) Fieser, Hershberg and Newman, This Journal, **57**, 1509 (1935); (c) Peak and Robinson, *J. Chem. Soc.*, 759 (1936); (d) Ruzicka, *Helv. Chim. Acta*, **19**, 419 (1936).

(5) (a) Mosettig and Duvall, This Journal, **59**, 367 (1937); (b) Wilds and Shunk, *ibid.*, **65**, 469 (1943); Cook and Schoental, *J. Chem. Soc.*, 288 (1945).

(6) Weiss and Sonnenschein, *Ber.*, **58**, 1043 (1925), report a m. p. of 128–131°.

The picrate crystallized from ethanol in orange-red, flat rods of m. p. 127–128°.

Anal. Calcd. for $C_{28}H_{19}O_8N_3$: C, 64.0; H, 3.6. Found: C, 64.4; H, 3.9.

2,3-Diphenyl-1,4-naphthoquinone (III).—The naphthol II (2 g.) was dissolved in acetic acid (50 cc.) and, after addition of potassium dichromate (2 g.) in acetic acid (30 cc.), heated to boiling for two minutes. Upon pouring onto ice, a yellow precipitate (1.7 g.) was obtained. It crystallized from ethanol in yellow prisms of m. p. 135–136°. An additional recrystallization from acetic acid raised the m. p. to 140–141°, as reported in the literature.[6] The yield of pure product was 1.2 g. (60%).

Anal. Calcd. for $C_{22}H_{14}O_2$: C, 85.1; H, 4.5. Found: C, 85.2; H, 4.7.

DANIEL SIEFF RESEARCH INSTITUTE
REHOVOTH, PALESTINE RECEIVED APRIL 17, 1946

The Resistance to Hydrogenation of β-Stenols in Ethyl Acetate with Adams Platinum Oxide Catalyst

BY SEYMOUR BERNSTEIN AND LOUIS DORFMAN

It is known that dehydroergostenol on hydrogenation with either platinum oxide in glacial acetic acid[1] or with palladium in ethyl acetate[2] affords α-ergostenol and not δ-ergostenol since the unhydrogenated double bond migrates to the α-position. It was therefore surprising to find that dehydroergostenol was not hydrogenated with platinum oxide catalyst in ethyl acetate and the starting material was recovered unchanged. Likewise β-ergostenol could not be hydrogenated under these conditions.

This hitherto unsuspected fact that β-stenols are resistant to hydrogenation with platinum oxide in ethyl acetate should prove useful in future synthetic and structural work in the steroid field, *e. g.*, in the cardiac aglucons.

LEDERLE LABORATORIES, INC.
PEARL RIVER, NEW YORK RECEIVED[3] APRIL 22, 1946

(1) Morrison and Simpson, *J. Chem. Soc.*, 1710 (1932).
(2) Windaus and Lüttringhaus, *Ann.*, **481**, 119 (1930).
(3) Original manuscript received September 19, 1945.

Some Substituted Acetophenones[1]

BY E. CAMPAIGNE AND WM. BRADLEY REID, JR.

Ortho- and *meta*-methyl- and *ortho-* and *meta*-phenylacetophenones, required in another investigation, were prepared from acetic anhydride by the low temperature Grignard procedure of Newman and Booth.[2] The required Grignard reagent and yield of the corresponding methyl ketones were as follows: *o*-tolylmagnesium bromide, 48.2%; *m*-tolylmagnesium bromide, 46.4%; *o*-xenylmagnesium iodide, 61.8%; *m*-xenylmagnesium iodide, 26.8%.

The biphenyl compounds, being new, were characterized by means of their crystalline semicarbazones and 2,4-dinitrophenylhydrazones.

Experimental

***o*-Phenylacetophenone.**—2-Iodobiphenyl was produced in 82.7% yield by the toluene extraction of a mixture obtained by treating a diazotized solution of 2-aminobiphenyl (Monsanto Chemical Company) with excess potassium iodide solution. The 2-iodobiphenyl was converted to the Grignard reagent and treated with acetic anhydride, yielding *o*-phenylacetophenone as a yellow oil, b. p. 104–105° at 1 mm. This oil yielded a semicarbazone in white plates, melting at 197°.

Anal.[3] Calcd. for $C_{15}H_{15}N_3O$: N, 16.59. Found: N, 16.67.

A 2,4-dinitrophenylhydrazone was also prepared, and obtained in light orange plates, melting at 169–170°.

Anal. Calcd. for $C_{20}H_{16}N_4O_4$: N, 14.88. Found: N, 14.83.

3-Iodobiphenyl.—Using the method of Elks, Haworth and Hey,[4] *m*-nitroaniline was converted to 3-nitrobiphenyl in 43% yield. This nitro-compound, which melted at 59–61°, was reduced to the amine by hydrogenation over Adams platinum oxide catalyst in portions in 98.5% yield. The 3-aminobiphenyl, after distillation at 177–178° at 18 mm. pressure, solidified to a white solid melting at 31–31.5°. A solution of 53 g. (0.314 mole) of 3-aminobiphenyl in 500 ml. of 1.3 *M* sulfuric acid was diazotized with a solution of 22.5 g. (0.326 mole) of sodium nitrite in 50 ml. of water. The solid yellow diazo salt that formed was stirred vigorously in 500 ml. of toluene while a solution of 100.5 g. (0.628 mole) of potassium iodide in 250 ml. of water was added over a period of thirty minutes. The temperature of the reaction was maintained at +5° during the addition. The resulting red complex slowly decomposed at room temperature, and the black toluene layer that separated after several hours was dried and distilled at reduced pressure. The fraction which boiled at 145–155° at less than 1 mm. was redistilled at this pressure, and 3-iodobiphenyl was collected as a yellow oil, boiling at 149–152°. The yield was 42 g. or 48% of theoretical.

Anal. Calcd. for $C_{12}H_9I$: I, 45.42. Found: I, 45.69.

***m*-Phenylacetophenone.**—The Grignard reagent was prepared from 3-iodobiphenyl and converted to *m*-phenylacetophenone by treatment with acetic anhydride. The ketone was obtained as a light yellow oil boiling at 148–151° at less than 1 mm. pressure. It readily formed a semicarbazone which was obtained as white plates, melting at 222–223°.

Anal. Calcd. for $C_{15}H_{15}N_3O$: N, 16.59. Found: N, 16.47.

The 2,4-dinitrophenylhydrazone was also obtained as orange needles, m. p. 191–192°.

Anal. Calcd. for $C_{20}H_{16}N_4O_4$: N, 14.88. Found: N, 14.68.

(3) All analyses are by Mrs. W. B. Reid, Jr., of this Laboratory.
(4) Elks, Haworth and Hey, *J. Chem. Soc.*, 1285 (1940).

DEPARTMENT OF CHEMISTRY
INDIANA UNIVERSITY
BLOOMINGTON, INDIANA RECEIVED APRIL 26, 1946

A Simple Purification Procedure for DDT[1]

BY KATHRYN H. COOK AND WALTER A. COOK

A survey of the literature on the new insecticide popularly known as DDT, discloses the fact

(1) Presented before the Division of Organic Chemistry at the Atlantic City Meeting of the American Chemical Society, April 11, 1946.

that the purification of this substance is not as readily accomplished as would be expected. That this is obviously the case, can be concluded from the recent studies on the chemical composition of technical DDT by Haller, Bartlett, Drake, Newman and associates, and reported melting point data by these and other investigators,[2] which values range from 105 to 109°. Moreover the fact that three grades of DDT are recognized by the War Production Board and the armed forces of this country is a further suggestion of difficulties involved in its purification. The writers have found that a simple extraction or washing process of technical or laboratory prepared DDT specimens will provide a grade of purity at least equal to the minimum limit prescribed for aerosol quality (m. p. 103°) and, in most instances a value of 105° or better. The details of the experimental purification procedure of a technical DDT specimen procured from a well-known supply distributor are given as follows.

One hundred grams of the technical product which melted at 60° is treated with 50 ml. of 95% ethyl alcohol to form a thick paste and then diluted with 300 ml. of water. This mixture is filtered on a Buchner, transferred to a 600 ml. beaker and treated with 250 ml. of 95% ethyl alcohol. After chilling in an ice–salt brine it was filtered and washed with an additional 100-ml. portion of cold alcohol. The alcohol extracted product is treated similarly with (30–60°) petroleum ether and after filtration, washing and drying, 65 g. of partially purified DDT m. p. (block value) 106–107° is obtained. The latter fraction on recrystallization from 800 ml. hot 95% ethanol gave 60 g. of product, m. p. 109.5–110° (cor.). This upon two additional and alternate petroleum ether extractions, and alcohol recrystallizations under conditions as described above, yielded 46 g. pure product m. p. 110–110.5° (cor.) in a Roth apparatus. Further purification attempts did not change this value. Needless to say in ordinary purification work, the products from the previous steps were not completely dried inasmuch as the efficiency of subsequent extractions is believed to be lowered due to decreased wetting effect of the solvent; furthermore less time is required in the purification process. Thus, the technical specimen referred to above contains approximately 67% DDT, and approximately 70% of the actual DDT is recovered. Cautious evaporation of the several extraction filtrates to remove the last traces of solvent reveals evidence in the residues of progressively decreasing quantities of contaminants together with some pure DDT.

Laboratory specimens prepared by a modification of the chlorosulfonic acid condensation,[3] and similarly purified as previously described, melted at 110–110.5° (cor.). Mixed melting point of the laboratory purified product and that isolated from technical DDT, showed no depression.

In order to establish further that the compound with m. p. 110–110.5° was pure DDT and not DDD[4] (1,1-di-*p*-chlorophenyl-2,2-dichloroethane), which melts also at 110.5–111°, a mixed melting point determination of both substances showed a marked depression. Additional evidence for the identification of our product (m. p. 110–110.5° cor.) as DDT is given in the following.

Anal.[5] Calcd. for $C_{14}H_9Cl_5$: C, 47.43; H, 2.56; Cl, 50.01. Found: C, 47.06; H, 2.76; Cl, 49.93.

A dinitro derivative[2] of our product melted at 148–148.5° (cor.). This value is in agreement with that reported by Haller and associates, and higher than the 143° value reported by Zeidler. In ordinary recrystallization operations in which large quantities of partially purified DDT are involved acetone is superior to alcohol inasmuch as less acetone is required and the contaminants are more soluble. For example, with 354.5 g. (1 mole) of partially purified DDT (m. p. 105–107°) dissolved in 1600 ml. acetone at room temperature, filtered and on slow addition of 400 ml. water with stirring, a product was obtained which upon drying weighed 335 g. (94.7% recovery); m. p. 109.5–110° (cor.). With alcohol in place of acetone as the solvent, at least two recrystallizations each with a solvent-volume, solute-weight ratio of approximately 10 to 1 were found necessary to achieve the same degree of purity. It should be noted, further, that the above described purification procedure is not intended to cover commercial dusting powders or artificially blended spray preparations containing DDT as one of the ingredients. Moreover, as a future primary reference standard for entomological and pharmacological studies, the product which melts at 110–110.5° (cor.) is recommended for acceptance.

(2) Haller, Bartlett, Drake, Newman and co-workers, THIS JOURNAL, **67**, 1591 (1945); Gooden, *ibid.*, **67**, 1617 (1945); Zeidler, *Ber.*, **7**, 1180 (1874); Bailes, *J. Chem. Ed.*, **22**, 122 (1945), and Gunther, *ibid.*, **22**, 238 (1945). The latter states that one to two recrystallizations from excess ethanol or isopropanol usually yields a m. p. of 105° and to secure a very pure product it is usually necessary to decolorize the material at least once with charcoal, followed by four or five recrystallizations.

(3) Rueggeberg and Torrans, *Ind. Eng. Chem.*, **38**, 211 (1946).

(4) Sample kindly supplied by Dr. William A. Mosher of Pennsylvania State College.

(5) Duplicate analyses were made and the average values for C, H and Cl reported here. Microanalyses by Dr. Carl Tiedcke.

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RECEIVED NOVEMBER 23, 1945

Specificity of the Action of Urease

BY CLARA L. DEASY

Urease catalyzes the hydrolysis of urea, but the enzyme has been shown to be without effect on a number of derivatives of urea.[1] This study was made to determine whether urease can catalyze the hydrolysis of guanylurea, or whether the action of urease on urea can be inhibited by guanylurea.

Experimental.—Guanylurea was used in the form of the commercially available sulfate,[2] which was recrystallized after treatment with bone charcoal. The urease solution was prepared according to the Folin–Wu method,[3] except that the concentration of the solution was increased by using five times the amount of jack bean meal.

The urea was used in 3% solution (30 mg./ml.); 5 ml. of water and 1 ml. of urease solution were added in each determination. The mixtures were incubated for fifteen minutes at 45–50°. Analysis of extent of hydrolysis was made according to the method of Marshall,[4] by titration with standard hydrochloric acid (0.09306 *N*) with methyl orange as indicator. Blanks were run on the urease, urea, guanylurea sulfate and guanylurea sulfate + urea, each incubated for fifteen minutes at 45–50° with 5 ml. of water. The necessary blanks were subtracted from the volume of standard hydrochloric acid used in each determination to give the corrected volume (Column 4, Table I). Each experiment is an average value of 4 determinations.

In experiment 1 the blanks for guanylurea sulfate and for urease exceeded by 0.03 ml. the volume of standard hydro-

(1) See, for example, Armstrong and Horton, *Proc. Roy. Soc.* (London), **B85**, 109 (1912); Cajori, *Proc. Soc. Exptl. Biol. Med.*, **30**, 184 (1932); Bonnet and Razafimahery, *Enzymologia*, 1, 55 (1936).

(2) Supplied through the courtesy of American Cyanamide and Chemical Corp.

(3) Peters and Van Slyke, "Quantitative Clinical Chemistry," Vol. II, Williams and Wilkins Co., Baltimore, Md., 1932, p. 545.

(4) Marshall, *J. Biol. Chem.*, **14**, 283 (1913).

TABLE I

No.	Guanylurea sulfate, mg.	Urea added, mg.	HCl, ml. cor.	Urea found, mg.
1	100	0	−0.03	..
2	0	30.0	10.68	29.8
3	100	30.0	10.62	29.7
4	100	30.0	10.36	28.9
5	100	30.0	10.39	29.0

chloric acid required for an end-point when guanylurea sulfate and urease were incubated together. Similar results were obtained when the incubation time for the mixture was increased to thirty minutes. In experiment 3 the urease was added to a mixture of guanylurea sulfate and urea. To determine whether the action of urease on urea would be influenced by previous treatment with guanylurea sulfate, the urease was added to the guanylurea sulfate in Expts. 4 and 5 and kept in contact with it at room temperature for five and for fifteen minutes, respectively, before the urea was added.

Results.—The experiments indicate that urease does not catalyze the hydrolysis of guanylurea sulfate. A solution of urease which has first been treated with guanylurea sulfate gives somewhat low values in the determination of urea; this effect is, however, very slight.

TEMPLE UNIVERSITY
SCHOOL OF MEDICINE
PHILADELPHIA 40, PA. RECEIVED APRIL 25, 1946

Picrolonates of Bufotenine, Bufotenidine and Dehydrobufotenine

BY VENANCIO DEULOFEU AND BLANCA BERINZAGHI

Following our work[1] on the basic constituents of the venom of some South American toads, we have prepared the picrolonates of the indolic bases present in toad venom.

The picrolonates of bufotenidine and dehydrobufotenine can be prepared and purified more easily than bufotenine picrolonate. Dehydrobufotenine can be isolated more readily as the picrolonate than as its picrate, from the final residual mother liquors of the toad venom when the bases are extracted according to our procedure.[1] Dehydrobufotenine picrolonate, however, has too high a melting point to be of ready use in identification.

Bufotenine Picrolonate.—Amorphous bufotenine from *B. arenarum* was dissolved in ethanol and treated with an small excess of picrolonic acid. By heating the acid dissolves and when the solution was cooled crystals were obtained melting not sharply at 110°. By recrystallizing from ethanol, small, yellow prisms, melting 120–121° were obtained.

Anal. Calcd. for $C_{12}H_{16}ON_2 \cdot C_{10}H_8O_5N_4$: N, 17.94. Found: N, 18.34.

Bufotenidine Picrolonate.—Bufotenidine iodide was obtained from amorphous bufotenine and methyl iodide according to Wieland, Konz and Mittasch,[2] and melted at 210°. The iodide was dissolved in a little amount of water and treated with a slight excess of picrolonic acid. This was dissolved by heating, and on cooling yellow prisms melting 253–255° were obtained. Recrystallized from 50% ethanol, the fine yellow needles melted 255°.

Anal. Calcd. for $C_{13}H_{18}ON_2 \cdot C_{10}H_8O_5N_4$: N, 17.42. Found: N, 17.14.

Dehydrobufotenine picrolonate was obtained by treating a water solution of dehydrobufotenine hydrochloride with an excess of picrolonic acid, heating to dissolution and cooling. The picrolonate precipitates and after crystallization from ethanol (50%) yellow prisms melting above 300° and darkening from 275° (quick heating) were obtained.

Anal. Calcd. for $C_{12}H_{14}ON_2 \cdot C_{10}H_8O_5N_4$: N, 18.02. Found: N, 17.99.

A similar picrolonate was obtained from the solution of crude bases of *B. arenarum* after separation of bufotenine.

FACULTAD DE CIENCIAS EXACTAS F. Y. N.
LABORATORIO DE QUÍMICA ORGÁNICA
BUENOS AIRES, ARGENTINA RECEIVED MARCH 20, 1946

(1) V. Deulofeu and E. Duprat, *J. Biol. Chem.*, **153**, 459 (1944).
(2) H. Wieland, W. Konz and H. Mittasch, *Ann.*, **513**, 1 (1934).

The Use of Liquid Phase Oxidation for the Preparation of Nuclearly Substituted Styrenes. II. *p*-Vinylphenyl Acetate

BY WILLIAM S. EMERSON, JOSEF W. HEYD, VICTOR E. LUCAS, WILLIAM B. COOK, GRAFTON R. OWENS AND ROBERT W. SHORTRIDGE

In a previous paper[1] we have shown that methyl *p*-ethylbenzoate is smoothly oxidized to methyl *p*-acetylbenzoate by air in the presence of chromium oxide and calcium carbonate. While the oxidation of *p*-ethylphenyl acetate to *p*-acetylphenyl acetate is a great deal more difficult, we have accomplished it successfully (24% conversion and 79% yield) by means of oxygen in the presence of a chromium oxide–cobalt hydrate–calcium carbonate catalyst. Any free phenol in the reaction mixture inhibits the oxidation altogether, so that its presence must be rigorously avoided.

The *p*-acetylphenyl acetate was smoothly hydrogenated in the presence of copper chromite to *p*-(α-hydroxyethyl)-phenyl acetate. Distillation of the latter compound from potassium bisulfate yielded 48% of *p*-vinylphenyl acetate based on this carbinol.

The authors are grateful to Dr. G. F. Deebel and Messrs. C. E. Wheelock, E. L. Ringwald and R. P. Haase for the preparation of considerable quantities of *p*-ethylphenol.

Experimental

***p*-Ethylphenol** was prepared essentially according to the method of Hartman.[2] One hundred fifty-two grams (58%) was obtained from the fusion of 450 g. of sodium *p*-ethylbenzenesulfonate with 300 g. of potassium hydroxide and 750 g. of sodium hydroxide. It boiled at 95–101° (10 mm.) (218.5–219.5°).[3]

***p*-Ethylphenyl Acetate.**—*p*-Ethylphenyl acetate was prepared by refluxing for six hours 713 g. of *p*-ethylphenol with 1 liter of acetic anhydride containing 100 g. of sodium acetate. The reaction mixture was diluted with water and benzene, the layers separated and the benzene layer dis-

(1) Emerson, Heyd, Lucas, Chapin, Owens and Shortridge, THIS JOURNAL, **68**, 674 (1946).
(2) Hartman, "Org. Syntheses," Coll. Vol. I, p. 175.
(3) Béhal and Choay, *Bull. soc. chim.*, [3] 11, 209 (1894).

tilled to obtain the product. The yield was 880 g. (92%), b. p. 120–121° (20 mm.), $n^{25}D$ 1.4977. Pure *p*-ethylphenyl acetate boiled at 113–114° (16 mm.), (226–227°),[4] $n^{25}D$ 1.4970, d^{25}_{25} 1.030.

Anal.[5] Calcd. for $C_{10}H_{12}O_2$: C, 73.3; H, 7.33. Found: C, 73.6; H, 7.60.

p-**Acetylphenyl Acetate.**—Oxygen was blown through an alundum disperser into 317 g. of *p*-ethylphenyl acetate containing 5% of a 1:1:8 mixture of chromium oxide, cobalt hydrate and calcium carbonate held at 140–145° for fifteen hours. Water was removed by means of a Dean and Stark trap. Upon cooling, the catalyst was removed by filtration and washed with benzene. The combined filtrate and washings were refluxed for two hours with 100 cc. of acetic anhydride containing 10 g. of sodium acetate. This mixture was washed thoroughly with water and then distilled to give 222 g. (70% recovery) of *p*-ethylphenyl acetate, b. p. 109–124° (13 mm.), $n^{25}D$ 1.4961, and 81 g. (24% conversion, 79% yield) of *p*-acetylphenyl acetate, b. p. 157–162° (13 mm.) [160° (22 mm.)].[6]

p-(α-Hydroxyethyl)-phenyl **Acetate.**—One hundred and nine grams of *p*-acetylphenyl acetate was hydrogenated (2000 lb. initial pressure) in the presence of 11 g. of copper chromite, at 130°. The hydrogenation was stopped as soon as one mole of hydrogen had been taken up. The hydrogenated product boiled at 138–142° (3 mm.), $n^{25}D$ 1.5160; yield was 86 g., 78%. An analytical sample boiled at 89–93° (0.07 mm.), $n^{25}D$ 1.5178, d^{25}_{25} 1.134.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.7; H, 6.67. Found: C, 66.2; H, 6.87.

A sample of this compound was acetylated. The main fraction of the product distilled at 94.5–98.0° (0.09 mm.), (b. p. 145–6° (7 mm.), m. p. 51°),[7] $n^{25}D$ 1.4980, d^{25}_{25} 1.128.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.9; H, 6.31. Found: C, 65.4; H, 6.48.

p-**Vinylphenyl Acetate.**[8]—Eighty-six grams of *p*-(α-hydroxyethyl)-phenyl acetate, 0.9 g. of potassium bisulfate, and 0.9 g. of hydroquinone were placed in a 500-ml. flask equipped with a Vigreux column and heated by an oil-bath. Hydroquinone was placed in the receiver. The product was distilled as formed at an oil-bath temperature of 175–200° and a pressure of 60-13 mm. This product was twice distilled in the presence of hydroquinone to yield 37 g. (45%) of *p*-vinylphenyl acetate; b. p. 100–105° (4 mm.), (b. p. 83–86° (1 mm.)),[7] $n^{25}D$ 1.5356, ($n^{25}D$ 1.5368),[7] d^{25}_{25} 1.065, (d^{25}_4 1.0586).[7]

Anal. Calcd. for $C_{10}H_{10}O_2$: C, 74.1; H, 6.18. Found: C, 73.8; H, 6.41.

(4) Clemmensen, *Ber.*, **47**, 53 (1914).

(5) All of the analyses are microanalyses performed by the Arlington Laboratories, Fairfax, Virginia.

(6) Verley, *Bull. soc. chim.*, [3] **19**, 140 (1898).

(7) Alderman and Hanford, U. S. Patent 2,276,138; *C. A.*, **36**, 4732 (1942).

(8) Essentially the method of Brooks, THIS JOURNAL, **66**, 1295 (1944).

CENTRAL RESEARCH DEPARTMENT
MONSANTO CHEMICAL COMPANY
DAYTON, OHIO

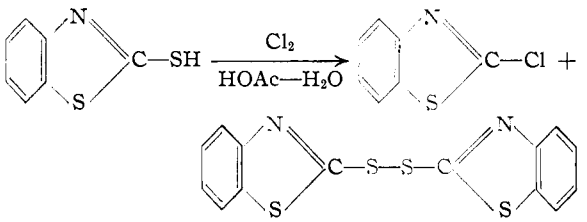
RECEIVED APRIL 5, 1946

The Action of Chlorine on 2-Mercaptobenzothiazole in Aqueous Acetic Acid

BY STEPHEN P. FINDLAY AND GREGG DOUGHERTY

The action of aqueous chlorine on sulfides and disulfides to produce sulfonyl chlorides and thence sulfonic acids is a familiar preparative method.[1,2,3] Under these conditions one mole of 2-mercaptobenzothiazole reacts with half a mole of chlorine to give the corresponding disulfide.[4] However, if the chlorination is conducted in aqueous acetic acid and an excess of the halogen is used, the sulfhydryl group is to a considerable extent replaced by chlorine. Besides 2-chlorobenzothiazole minor quantities of bisbenzothiazolyl 2,2′-disulfide, bisbenzothiazolyl 2,2′-monosulfide, water soluble dyes, and tarry products are formed.

The chlorination of the thiazole in aqueous acetic acid is an exothermic reaction and the best yields of 2-chlorobenzothiazole were obtained when the admission of chlorine to the reaction mixture was so slow that the temperature did not rise above 45°.



Experimental

2-Mercaptobenzothiazole was obtained by treating the commercial product (Captax) with sodium carbonate solution, filtering off the insoluble material, acidifying the filtrate, and separating the precipitated mercaptan. This material after one recrystallization from glacial acetic acid melted at 174–176°.[5]

Procedure.—In a typical run gaseous chlorine was passed slowly for twenty-four hours through a mixture of 50 g. of 2-mercaptobenzothiazole in 200 ml. of glacial acetic acid and 50 ml. of water. The dark-brown product was poured into 350 ml. of water and, after stirring, the heavier phase was separated and steam distilled. The distillate was saturated with salt and extracted with ether. On standing long, pale yellow filaments of the monosulfide separated from the lighter phase and, after two recrystallizations from benzine (b. p. 70°), gave 0.07 g. of pure product, m. p. 99°. Admixture of this with an authentic sample of dibenzothiazolyl 2,2′-monosulfide, prepared by heating in absolute alcohol equimolecular quantities of **2-chlorobenzothiazole** and the potassium salt of 2-mercaptobenzothiazole in the presence of a trace of potassium iodide, did not depress the melting point. Removal of the ether from the extract gave 24 g. (yield 47%) of **2-chlorobenzothiazole**, b. p. 116–122° (3 mm.) and 248° (760 mm.), which, according to Hofmann's directions,[6] yielded a 6-nitro derivative, m. p. 190°. During the steam distillation about 7% of this was hydrolyzed to the hydroxy derivative.

A tarry residue after the steam distillation when recrystallized twice from benzene gave 3.1 g. (6.2%) of **dibenzothiazolyl 2,2′-disulfide**, m. p. 178°.

(1) Lee and Dougherty, *J. Org. Chem.*, **5**, 81–85 (1940).

(2) Schiller and Otto, *Ber.*, **9**, 1638 (1876).

(3) Douglass and Johnson, THIS JOURNAL, **60**, 1486 1489 (1938).

(4) U. S. Patent 2,265,347.

(5) All melting points are uncorrected.

(6) Hofmann, *Ber.*, **13**, 10 (1880).

FRICK CHEMICAL LABORATORY
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PRINCETON, N. J.

RECEIVED APRIL 15, 1946

Crystalline Racemic Calcium Pantothenate

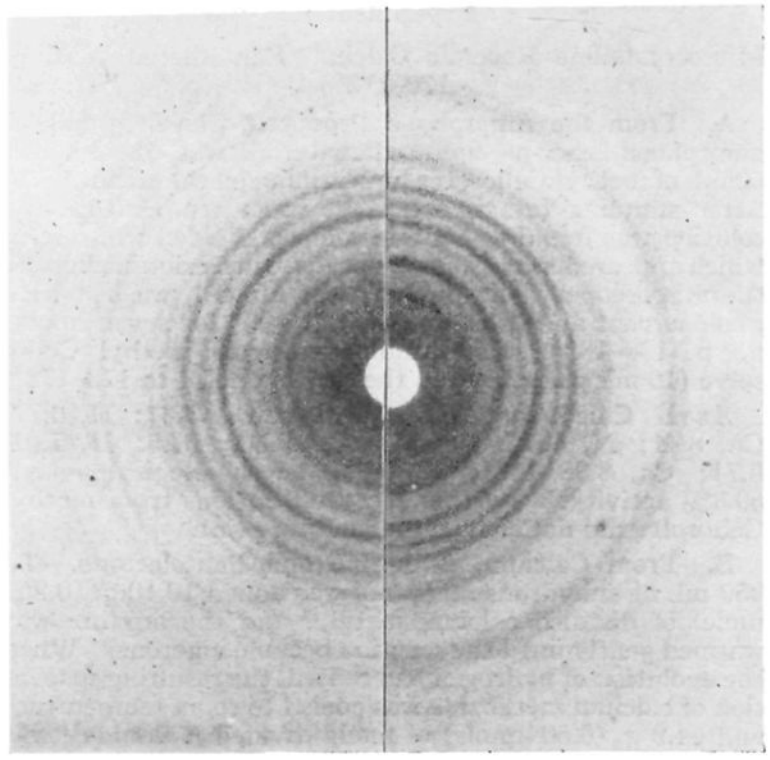
BY JARED H. FORD

The preparation of macrocrystalline calcium (+)-pantothenate has been reported by Levy,

Weijlard and Stiller.[1] Although racemic calcium pantothenate has been prepared by several investigators[2,3,4] no data have been reported which would lead one to believe that crystalline products were obtained. The preparation of pure microcrystalline racemic calcium pantothenate and a macrocrystalline methanol solvate are described in this communication.

Microcrystalline racemic calcium pantothenate was first obtained by dissolving an amorphous ether-precipitated sample[5] in methyl Cellosolve and allowing the solution to stand at room temperature for several weeks. The resulting white powder appeared as slender needles under a microscope and was found to have 50% activity.[6] After recrystallization from methyl Cellosolve it melted at 170–172°. When this microcrystalline product was dissolved in methanol and seeded with macrocrystalline calcium (+)-pantothenate[1] a fluffy mass of needle shaped crystals, some of which were large enough to be seen with the naked eye, formed very slowly. These proved to be a solvate which readily lost all of its methanol upon drying *in vacuo*, forming a microcrystalline product, melting point 187–189°, which also had 50% activity. It is interesting to note that calcium (+)-pantothenate has also been reported to crystallize from methanol as a solvate. Recrystallization of the higher melting product from methyl Cellosolve converted it into the lower melting form.

Both of the microcrystalline products appeared as slender needles under the microscope, but the crystals of the lower melting form were much smaller than those of the higher melting form. A mixture of the 170–172° and 187–189° products melted at 170–187°. Both forms had approximately the same solubility in methyl Cellosolve and both were found to be very soluble in methanol at room temperature if they were shaken vigorously so that solution occurred before crystals of the methanol solvate began to form (see Table I). The possibility that the difference in melting points was caused by an impurity seems unlikely in view of the fact that both forms could be recrystallized to constant melting points and that satisfactory analyses, both chemical and biological, were obtained in each case. The X-ray



M. p. 170–172° M. p. 187–189°

Fig. 1.

powder diagrams (see Fig. 1) indicate clearly that the two forms have different crystal structures.

TABLE I

APPROXIMATE SOLUBILITY[a] OF VARIOUS FORMS OF RACEMIC CALCIUM PANTOTHENATE AT ROOM TEMPERATURE

	Methyl cellosolve	Methanol
Amorphous	>50	>50.0
M. p. 170–172°	0.6	>50.0
M. p. 187–189°	0.6	>12.0
Methanol solvate	....	1.6[b]

[a] Solubility expressed in grams of solute per 100 ml. of solvent. [b] Solubility expressed in solvent-free material. Composition of the solvate not determined.

A convenient method for preparing methanol solutions of calcium pantothenate from metallic calcium, β-alanine and pantolactone is described in the experimental part.[7] By seeding these methanol solutions, pure racemic calcium pantothenate can be obtained in 70–80% yield. Thus it is now possible to make a pure crystalline product without resolving the pantolactone.

Acknowledgments.—The author wishes to express his thanks to Mr. Anthony Bucci for technical assistance, to Mr. Harold Buskirk and Miss Mary Katherine Gee for the microbiological assays, to Dr. George Pish and Mr. Norman Drake for the X-ray powder diagrams, and to Mr. Harold Emerson, Mr. William A. Struck and Miss Celia Triemstra for the microanalyses.

(1) Levy, Weijlard and Stiller, THIS JOURNAL, **63**, 2846 (1941).

(2) Williams, Mitchell, Weinstock and Snell, *ibid.*, **62**, 1784 (1940).

(3) Stiller, Harris, Finkelstein, Keresztesy and Folkers, *ibid.*, **62**, 1785 (1940).

(4) Barnett and Robinson, *Biochem. J.*, **36**, 357 (1942).

(5) Barnett and Robinson[4] reported that they obtained amorphous racemic calcium pantothenate having the theoretical 50% activity[6] by condensing racemic pantolactone (α-hydroxy-β,β-dimethyl-γ-butyrolactone) with the calcium salt of β-alanine in methanol solution and precipitating the product by adding the solution to 6 volumes of dry acetone or ether. In the present investigation numerous attempts were made to duplicate this work but the resulting amorphous products had only 38–44% activity.

(6) Biological activity in comparison with that of pure calcium (+)-pantothenate. Calcium (−)-pantothenate has been reported to be inactive.[1,3]

(7) A similar method has been described by Carlson and Safir in Canadian Patent 417,271 which was issued after the completion of the author's experimental work.

Experimental[8]

Microcrystalline Racemic Calcium Pantothenate (M. p. 170–172°)

A. From the Amorphous Product.—Eleven grams of amorphous ether-precipitated material[4] was dissolved in 50 ml. of methyl Cellosolve by warming on the steam-bath. After standing for six weeks at room temperature the solution was found to contain a finely divided white solid which appeared as very small needles when examined under the microscope. The product was filtered, washed with fresh solvent and dried *in vacuo* at 100° for seven hours; m. p. 166–168°. Recrystallization from methyl Cellosolve (10 ml. per g.) raised the melting point to 170–172°.

Anal. Calcd. for $C_{18}H_{32}N_2O_{10}Ca$: C, 45.37; H, 6.77; Ca, 8.41; N, 5.88. Found: C, 45.50, 45.25; H, 7.01, 6.71; Ca, 8.38, 8.21; N, 5.69; microbiological assay,[9] 50.3% activity.[6] Further recrystallizations from methyl Cellosolve did not change the melting point.

B. From Calcium, β-Alanine and Pantolactone.—To 250 ml. of anhydrous methanol was added 10.10 g. (0.252 mole) of distilled calcium metal,[10] and the mixture was warmed gently until the reaction became vigorous. When the evolution of hydrogen had ceased, the resulting suspension of calcium methoxide was cooled to room temperature and 44.9 g. (0.504 mole) of finely divided β-alanine[11] was added. The resulting mixture was stirred mechanically until a clear solution was obtained (about thirty minutes). A solution of 69.0 g. (0.530 mole) of racemic pantolactone (b. p. 119–122.5° (12.5 mm.)) in 500 ml. of methyl Cellosolve was then added and the methanol was distilled off *in vacuo*. The residual methyl Cellosolve solution was seeded with the crystals described in the preceding paragraph. After standing one month at room temperature, the product was filtered, washed with fresh solvent and dried *in vacuo* at 100°. The yield was 93 g. (77.5%); m. p. 166–169°. Recrystallization from methyl Cellosolve raised the melting point to 170–172°.

Microcrystalline Racemic Calcium Pantothenate (m. p. 187–189°)

A. From the 170–172° Melting Product.—Three grams of the above described microcrystalline salt was dissolved in 10 ml. of dry methanol at room temperature and seeded with crystalline calcium (+)-pantothenate.[1] On standing at room temperature, well defined colorless needles crystallized from the solution. After standing for eleven days the resulting thick slurry of the methanol solvate was filtered, washed with methanol and dried to constant weight *in vacuo* at 100°; m. p. 185–187°. After recrystallization from methanol (5 ml. per g.) it melted at 187–189°.

Anal. Calcd. for $C_{18}H_{32}N_2O_{10}Ca$: C, 45.37; H, 6.77; Ca, 8.41; N, 5.88. Found: C, 45.51; H, 6.58; Ca, 8.59; N, 6.07; microbiological assay, 52.8% activity. Further recrystallizations from methanol did not change the melting point.

B. From Calcium, β-Alanine and Pantolactone.—The methanol solution was prepared by the same method as that described above using 50.10 g. (1.25 mole) of calcium, 222.8 g. (2.50 mole) of β-alanine, 328.5 g. (2.525 mole) of racemic pantolactone (m. p. 84–85°)[12] and 2.5 liters of dry methanol. The solution was seeded with some of the crystals described in the preceding paragraph. After standing for six weeks at room temperature the resulting slurry was filtered, washed with methanol and dried *in vacuo* at 100° for eight hours. The yield was 419 g. (70%); m. p. 180–184°.

Anal. Calcd. for $C_{18}H_{32}N_2O_{10}Ca$: Ca, 8.41. Found: Ca, 8.39; microbiological assay, 47.2% activity.

The time required for the above recrystallizations may be shortened considerably by operation at slightly elevated temperatures (30–40°). Cooling to 0° was found to inhibit the crystallization completely.

RESEARCH LABORATORIES, THE UPJOHN COMPANY
KALAMAZOO, MICHIGAN RECEIVED[13] MAY 9, 1946

(8) Melting points on calcium pantothenate depend somewhat upon the rate of heating. Those reported in this paper were taken on finely powdered samples in Pyrex capillary tubes with the bath temperature increased at about 2° per minute.

(9) Strong, Feeney and Earle, *Ind. Eng. Chem., Anal. Ed.*, **13**, 566 (1941).

(10) Obtained from the Electro Metallurgical Company, 30 E. 42nd St., New York, N. Y.

(11) Ford, THIS JOURNAL, **67**, 876 (1945).

(12) Pure racemic pantolactone melts at 90–91°. See Ford, THIS JOURNAL, **66**, 20 (1944).

(13) Original manuscript received May 24, 1945.

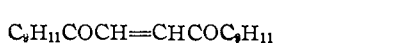
Coupling of Aryl Methyl Ketones by the Action of Sodium Hypohalite Solutions

BY REYNOLD C. FUSON AND ROBERT JOHNSON

When it was discovered that the diiodo derivatives of highly hindered aryl methyl ketones could be made by treating the ketones with limited amounts of sodium hypoiodite[1] an attempt was made to prepare the corresponding chloro iodo ketones by subjecting the monochloro ketones to the action of the hypoiodite. When the reaction was tried with α-chloroacetomesitylene, however, it was found to take a different course. Treatment with sodium hypochlorite or hypobromite converted the ketone to a halogen-free compound which proved to be the coupling product, *sym*-dimesitoylethylene (I). Both this compound and the ethane made from it by reduction had properties which corresponded to those reported by Conant and Lutz.[2]

It was found that acetophenone could be coupled in a similar manner. The product in this case, however, was the oxide (II) of the expected olefin, *sym*-dibenzoylethylene. The oxide had been made earlier by Lutz and Wilder.[3] Its structure was confirmed by synthesis. It was made by the action of phenylglyoxal on phenacyl bromide.[4]

II



I

Experimental

α-Chloroacetomesitylene and Sodium Hypoiodite.—Twenty grams of iodine dissolved in aqueous potassium iodide solution was added slowly, with stirring, to a mixture of 5 g. of α-chloroacetomesitylene, 100 ml. of 10% sodium hydroxide solution, 150 ml. of water and 70 ml. of dioxane. The addition was complete in thirty minutes. The product obtained by ether extraction was recrystallized from methanol and then from ethanol. The product melted at 173–174.5° and was shown by the mixed melting point method to be identical with the *sym*-di-(2,4,6-trimethylbenzoyl)-ethylene previously prepared by Conant and Lutz.[2] By use of the method of these authors the ethylene was reduced to the ethane melting at 136–137.5°.

By using sodium hypochlorite and α-chloroacetomesitylene a similar result was obtained. The yield of the ethyl-

(1) Johnson and Fuson, THIS JOURNAL, **57**, 919 (1935).

(2) Conant and Lutz, *ibid.*, **45**, 1303 (1923).

(3) Lutz and Wilder, *ibid.*, **56**, 1987 (1934).

(4) Bodforss, *Ber.*, **51**, 192 (1918); Kleucker, *ibid.*, **55B**, 1634 (1922).

ene from 10 g. of chloro ketone was 1 g. melting at 173–174.5°. The synthesis was carried out in two ways.

(a) From **Phenylglyoxal and Phenacyl Bromide.**—One gram of phenylglyoxal was added rapidly, with vigorous stirring, to a mixture of 20 ml. of 10% sodium hydroxide solution, 15 ml. of dioxane and 3 g. of phenacyl bromide. After being stirred for fifteen minutes the mixture was shaken with ether. Evaporation of the ether gave a small quantity of solid which upon purification by recrystallization from ethanol, proved to be *sym*-dibenzoylethylene oxide.

(b) From *sym*-**Dibenzoylethylene.**—A mixture of *sym*-dibenzoylethylene, dioxane, 10% sodium hydroxide solution and sodium hypochlorite solution was shaken for a short period of time. An appreciable quantity of the oxide was removed by ether extraction.

Acetophenone and Sodium Hypoiodite.—A mixture of 20 g. of acetophenone, 30 ml. of dioxane and 200 ml. of 10% sodium hydroxide solution was stirred vigorously in the cold during the addition of 50 g. of iodine in aqueous potassium iodide solution. The addition was completed in one to two hours. The reaction mixture was extracted with benzene, and the residue obtained by distilling the benzene was freed from iodoform by steam distillation. From the residue by recrystallization from ethanol was obtained a small amount of a compound melting at 128–129°.[3]

Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.11; H, 4.76. Found: C, 76.0; H, 5.0.

It has been reported[5] that *sym*-dibenzoylethylene forms in 58–71% yields when phenacyl chloride is treated with aqueous potassium hydroxide. Attempts to use this method to make the mesityl analog, however, were unavailing. Treatment of α-chloroacetomesitylene in dioxane with 10% aqueous sodium hydroxide solution, alcoholic potassium hydroxide solution or sodium ethoxide failed to yield any *sym*-dimesitoylethylene.

(5) Bogoslov, *J. Gen. Chem. U. S. S. R.*, **14**, 993 (1944); *C. A.*, **39**, 600 (1945).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS

RECEIVED MARCH 30, 1946

Effect of Phenylacetic Acid Derivatives on the Types of Penicillin Produced by Penicillium Chrysogenum Q176

BY K. HIGUCHI, F. G. JARVIS, W. H. PETERSON AND M. J. JOHNSON

Because of recent emphasis on the differences in *in vivo* behavior among the various penicillins, data on the relative amounts of the penicillins produced by *P. chrysogenum* Q176 under various conditions become of interest. Some of our recent pertinent data are therefore summarized in Table I. The assay used to differentiate the penicillins is a microbiological procedure involving the use of four organisms, which will be published elsewhere. On known mixtures of three penicillins (G, X and K), the assay has given an average error of 10% in the estimation of the quantity of one component. Yields in the table are expressed as *S. aureus* units.

The following conclusions may be drawn from the table: (1) The penicillin produced in the absence of phenylacetic acid derivatives is largely K. Although the remainder has been calculated as G, its amount is too small to permit confidence in the result. (2) In the presence of corn steep liquor, which is known to contain phenylacetic acid derivatives, the proportion of G produced increases. The production of G is greatest early in the fermentation. (3) In the presence of added phenylacetic acid derivatives there is a great increase in the proportion of G. (4) The addition of a phenylacetic acid derivative always results in an increase in unit yield (and a larger increase in molar yield). (5) The addition of *p*-hydroxyphenylacetic acid results in the production of significant amounts of penicillin X, but phenylacetic

TABLE I

EFFECT OF PHENYLACETIC ACID DERIVATIVES ON PENICILLIN PRODUCTION

Run no.[a]	Compound added[c]	Age of fermentation, hr.	Total penicillin, u./ml.	Composition of penicillin, % G	X[b]	K
1	None	42	94	13	...	87
		66	233	14	...	87
		75	264	12	...	88
	β-Phenylethylamine	42	117	91	...	9
		66	272	76	...	24
		90	435	66	...	34
	Phenylacetic acid[d]	42	169	88	...	12
		66	333	79	...	21
		75	387	74	...	26
	Phenylacetamide	42	119	91	...	9
		66	194	69	...	31
		90	384	57	...	43
2	None	60	161	44	3	53
		108	569	29	1	70
	β-Phenylethylamine	60	267	93	2	5
		108	726	78	5	17
	Phenylacetamide[d]	60	335	103	1	− 4
		108	616	78	2	20
	Phenylacetic acid[d]	60	448	109	3	−12
		108	673	76	−1	25
	p-Hydroxyphenylacetic acid	60	195	57	18	25
		108	422	42	11	47
	p-Hydroxyphenylacetic acid[d]	60	209	39	26	35
		108	462	34	10	56
3	None	49	638	30	...	70
4	Phenylacetic acid[e]	24	216	35	...	65
		60	1000	67	...	33
		72	1045	77	...	23

[a] Runs 1 and 2 were carried out in 500-ml. Erlenmeyer flasks containing 85 ml. (run 1) or 100 ml. (run 2) of medium. The medium used in run 1 consisted of the following constituents in grams per liter: lactose 22.5; glucose 7.5; ammonium lactate 7.1; potassium dihydrogen phosphate 2.0; magnesium sulfate 0.25; ferrous sulfate 0.20; copper sulfate 0.005; zinc sulfate 0.02; aluminum chloride 0.00027; potassium dichromate 0.000053. The medium used in run 2 contained the following constituents in grams per liter: corn steep liquor solids 30; lactose 30; calcium carbonate 10. Runs 3 and 4 were carried out in aerated and agitated tanks. The volume of medium used was 220 liters. The medium used in run 3 contained in grams per liter: steep liquor solids 40; lactose 40; calcium carbonate, 10; sodium sulfate 1.0. The medium used in run 4 was the same as that in run 3 except that the steep liquor concentration was 20 g. per liter. [b] When the differential assay results were calculated as a mixture of G and K only, no figure is given for X. [c] The compounds were added at a level of 0.5 g. per liter, and were added before sterilization unless otherwise stated. [d] The compound was added twenty-four hours after inoculation. [e] The phenylacetic acid was added in 6 equal portions, at 0, 12, 24, 36, 48 and 60 hours.

acid appears to be more available to the organism as a precursor than the hydroxy derivative.

DEPARTMENT OF BIOCHEMISTRY
UNIVERSITY OF WISCONSIN
MADISON, WISCONSIN RECEIVED JUNE 13, 1946

The Molecular Size and Shape of Botulinus Toxin[1]

BY GERSON KEGELES[2]

Type A Botulinus toxin has been prepared in crystalline form by two independent groups of workers.[3,4] Concurrent with fractionation studies by these groups, the physicochemical properties of the toxin were investigated.[5] Electrophoretic investigations are reported elsewhere.[4] This communication reports conclusions as to the size and shape of the toxin molecule, based on studies of diffusion, apparent specific volume, and viscosity performed on crystalline materials.

The diffusion measurements were carried out in 0.06 molar sodium acetate buffer at *p*H 4.48 in the Tiselius electrophoresis apparatus[6] as described by Longsworth.[7] The results appear in Table I, where the diffusion constants have been averaged from both channels.

TABLE I

Da is calculated from height and area; *Dm* calculated by method of moments; $D_{20,w}$ calculated from average of *Da* and *Dm*.

Source	C-50 (Lamanna)[3]	XII (Abrams)[4]	XII (Abrams)[4]
Protein concn., %	0.47	0.98	0.50
Temp., °C.	1.0	1.0	20.0
$Da(10)^7$ cm.²/sec.	0.93	1.04	1.99
$Dm(10)^7$ cm.²/sec.	0.95	1.22	2.00
$D_{20,w}(10)^7$ cm.²/sec.	1.79	2.16	2.10

The lower value observed for the electrophoretically homogeneous fraction C-50 may be due, possibly, to partial denaturation resulting from the use of chloroform in its purification.

Density measurements on fractions prepared by both methods were made in an uncapped pycnometer at 30°. Since the protein becomes insoluble when dried, solutions for density determinations were prepared by dialysis against the buffers used as reference solvents. Protein concentrations in these solutions were determined by Kjeldahl nitrogen, using 14.2% as the best available figure for nitrogen content.[3,4] Apparent specific volumes in 0.06 molar sodium acetate buffer at *p*H 4.48 varied somewhat with concentration. On the assumption that the variation was a charge effect, the density measurement was repeated nearer to the isoelectric point[4] in the presence of a large excess of salt. The apparent specific volume obtained for a 0.59% solution of the salt-fractionated protein[4] in 0.2 molar sodium chloride–0.02 molar sodium acetate buffer at *p*H 5.38 was 0.76. The value of the partial specific volume corrected[8] to 20° is taken as $V_{20} = 0.75_5$.

Viscosity measurements at seven protein concentrations from 0.1 to 0.8 per cent. by weight in 0.06 molar sodium acetate buffer at *p*H 4.48 were made with an Ostwald viscometer, using fractions prepared by both methods. Although subsequent examination revealed extensive electrophoretic inhomogeneity in the crystalline chloroform-treated protein fraction studied,[3] satisfactory agreement in the viscosity data was obtained, giving an intrinsic viscosity of 10.6. This corresponds to an axial ratio of 8.3 according to the Simha theory[9] for elongated ellipsoids and a frictional ratio f/f_0 of 1.45 from the Perrin theory.[10] The isoelectric point[4] is 5.60 and further addition of neutral salt would suppress charge effects, giving a lower value for the frictional ratio.

The molecular weight *M* is 1,130,000 as calculated from the diffusion constant $D_{20,w} = 2.10(10)^{-7}$ cm²/sec., the partial specific volume $V_{20} = 0.75_5$ and the frictional ratio $f/f_0 = 1.45$ with the equation[11]

$$MV_{20} = [2.89(10)^{-5}/D_{20,w}(f/f_0)]^3$$

This must be regarded as a lower limit, because the error in the frictional ratio is tripled by this method of calculation. It is hoped that future ultracentrifuge studies which were not possible at the time of this investigation will improve the accuracy of the data. The large size of the molecule is particularly surprising in view of previous studies on bacterial toxins.[12]

(1) Investigations conducted at Camp Detrick, Frederick, Maryland, from July through October, 1945, by Gerson Kegeles, 1st Lt., CWS.

(2) Present address: Chemistry Department, University of Wisconsin, Madison, Wisconsin.

(3) Lamanna, McElroy and Ecklund, *Science*, **103**, 613 (1946).

(4) Abrams, Kegeles and Hottle, *J. Biol. Chem.*, **164**, 63 (1946).

(5) The author is indebted to the senior author of each group for the materials for these studies.

(6) Tiselius, *Trans. Faraday Soc.*, **33**, 524 (1937).

(7) Longsworth, *Ann. N. Y. Acad. Sci.*, **41**, 267 (1941).

(8) Svedberg and Pedersen, "The Ultracentrifuge," Oxford Press, 1940, Appendix II.

(9) Simha, *J. Phys. Chem.*, **44**, 25 (1940).

(10) Perrin, *J. phys. rad.* **VII**, **7**, 1 (1936).

(11) Reference 8, equation (70a).

(12) Krejci, Stock, Sanigar and Kraemer, *J. Biol. Chem.*, **142**, 735 (1942).

LABORATORIES, TECHNICAL DEPARTMENT
CAMP DETRICK
FREDERICK, MARYLAND RECEIVED JUNE 8, 1946

Preparation of *p*-Alkylbenzyl Chlorides

BY G. M. KOSOLAPOFF

The preparation of *p*-alkylbenzyl chlorides has been effected usually by the method of Blanc[1] or by minor variations thereof. Such procedures utilize the catalytic effect of zinc chloride, which necessitates rather strict temperature control to avoid resinification and, generally, polysubstitu-

(1) Blanc, *Bull. soc. chim.*, (4) **33**, 313 (1923).

tion. Furthermore, the zinc chloride has to be removed with scrupulous and time-consuming aqueous washing in order to avoid decomposition of the products on distillation. It was found that much of the tedium of these preparations can be avoided by the use of a procedure which is in essence that of Cambron.[2] With elimination of the zinc chloride the usually troublesome emulsion formation on washing is avoided, the necessity for close temperature control is eliminated and the yields on reacted hydrocarbon are ample for most purposes. The following examples illustrate the procedure.

Experimental

p-**Ethylbenzyl Chloride.**—238 g. of ethylbenzene, 90 g. of paraformaldehyde, 250 g. of glacial acetic acid, 280 cc. of concentrated hydrochloric acid and 135 cc. of 85% phosphoric acid were agitated at 100° (steam-bath) for four and one-half hours. On cooling the organic layer was separated, washed three times with cold water and distilled to yield 114 g. of recovered ethylbenzene, b. p. 42° at 28 mm., and 132 g. of *p*-ethylbenzyl chloride, b. p. 111° at 26 mm., $n^{25}D$ 1.5290, for 38% conversion and 73% yield.

p-**Butylbenzyl Chloride.**—96 g. of *n*-butylbenzene, 29 g. of paraformaldehyde, 79 g. of glacial acetic acid, 88 cc. of concentrated hydrochloric acid and 43 cc. of 85% phosphoric acid were stirred under reflux for sixteen hours. On cooling, the organic layer was separated and washed three times with cold water. On distillation there was obtained 69.5 g. of recovered *n*-butylbenzene and 24 g. of *p*-butylbenzyl chloride, b. p. 142–146° at 27 mm., $n^{25}D$ 1.5159, for 27.5% conversion and 67% yield.

(2) Cambron, *Can. J. Research*, **17B**, 10 (1939).

MONSANTO CHEMICAL COMPANY
CENTRAL RESEARCH DEPARTMENT
DAYTON 7, OHIO

RECEIVED APRIL 4, 1946

The Toxicity of 3-Fluoro-*d*(+)- and *l*(−)-tyrosine

BY CARL NIEMANN AND M. M. RAPPORT

The toxicity and physiological action of 3-fluoro-*dl*-tyrosine have been the subject of numerous investigations[1] and in view of the interest shown in this substance it appeared desirable to compare the toxicity of the *d*- and *l*-isomers with that of the *dl*-mixture.[2] The *d*- and *l*-isomers were obtained from the *dl*-mixture by adoption of the method of enzymatic resolution originally developed by Bergmann and co-workers.[3]

In the rat the toxicity of each antipode was found to be identical with that of the *dl*-mixture and one may conclude that antipodal specificity with reference to the amino side chain is not a critical factor in the toxic action of 3-fluorotyrosine. One cannot conclude that the amino acid side chain is without effect, as *o*-fluorophenol is much less toxic than is 3-fluorotyrosine.[4] It appears that the presence of the amino acid side chain denies to 3-fluorotyrosine the detoxification routes ordinarily available to phenols with the result that the rat is forced to metabolize 3-fluorotyrosine with the concomitant formation of toxic end products other than fluoride ion.[1a] It appears from the work of Niedner[1b] that 3-fluorotyrosine behaves similarly in the mouse, for the LD_{50} for the mouse is apparently equal to that for the rat.

Experimental

N-Benzoyl-3-fluoro-*dl*-tyrosine.—3-Fluoro-*dl*-tyrosine[2] (20 g.) was benzoylated following the procedure of Carter and Stevens[5] to give 20.1 g. (66%) of N-benzoyl-3-fluoro-*dl*-tyrosine, m. p. 178–179° after recrystallization from a mixture of ethyl acetate and ligroin.

Anal. Calcd. for $C_{16}H_{14}O_4NF$ (303); C, 63.4; H, 4.7; N, 4.6. Found: C, 63.5; H, 4.4; N, 4.5.

3-Fluoro-*l*(−)-tyrosine.—N-Benzoyl-3-fluoro-*dl*-tyrosine (8.75 g.) was dissolved in 35 ml. of *N* sodium hydroxide and 44 ml. of 2 *M* sodium acetate and the solution filtered prior to the addition of 88 ml. of 0.1 *M* citrate buffer (*p*H 5.0), 0.65 g. of cysteine hydrochloride, 5.25 ml. of aniline, 88 ml. of a filtered papain solution prepared by dissolving 0.9 g. of purified papain[3a] in 100 ml. of 0.05 *M* citrate buffer (*p*H 5.0) and 170 ml. of water. After the addition of 1 ml. of 50% acetic acid the solution (*p*H 5.8) was incubated at 40° for seven days adding 1 ml. of 50% acetic acid on the second and third days. The precipitate was collected, washed with cold water and 50% aqueous ethanol and dried to give 3.25 g. of crude N-benzoyl-3-fluoro-*l*(−)-tyrosylanilide, m. p. 194–197° dec. The filtrate obtained after the removal of the precipitated anilide was adjusted to *p*H 5.5 with 50% acetic acid and incubated at 40° for another week. A second crop of 1.70 g. of anilide, m. p. 192–196°, was obtained to give a total yield of 4.95 g. or 91% of the theoretical quantity. A suspension of 4.95 g. of the above anilide in 200 ml. of 10% hydrochloric acid was refluxed for eighteen hours, the hydrolysate cooled to 25°, filtered and the filtrate extracted with ether. The aqueous phase was concentrated *in vacuo* to 50 ml. and neutralized by the addition of sodium acetate. The addition of ether to the solution induced crystallization whereupon the ethereal phase was decanted, the product collected and recrystallized twice from water to give 1.2 g. (48%) of 3-fluoro-*l*(−)-tyrosine, m. p. 278–279° with decomposition starting at 265° when heated at the rate of 5°/min.

Anal. Calcd. for $C_9H_{10}O_3NF$ (199): C, 54.3; H, 5.1; N, 7.0. Found: C, 54.5; H, 5.2; N, 6.9: $[\alpha]^{26}D = \frac{-0.29 \times 1.95}{1 \times 0.100} = -5.7°$ (in 4% hydrochloric acid).

3-Fluoro-*d*(+)-tyrosine.—The filtrate remaining after the removal of the second crop of N-benzoyl-3-fluoro-*l*(−)-tyrosylanilide was acidified with concd. hydrochloric acid to *p*H 1–2 and exhaustively extracted with ethyl acetate. The ethyl acetate phase was dried over sodium sulfate, the solvent removed and the residual oil refluxed with 200 ml. of 10% hydrochloric acid for eighteen hours. The hydrolysate was treated as described above and 2.2 g. of a mixture of 25% of 3-fluoro-*l*(−)-tyrosine and 75% of 3-fluoro-*d*(+)-tyrosine was obtained. This product was dissolved in the minimum quantity of hot water, the solution cooled, the precipitate discarded and the filtrate evaporated to dryness. The residue was recrystallized from water to give 0.9 g. of 3-fluoro-*d*(+)-tyrosine, m. p. 279–

(1) See for example (a) P. Boyer, R. Evans and P. Phillips, *J. Pharmacol. Exptl. Therap.*, **73**, 176 (1941); (b) K. Niedner, *Z. Krebsforsch.*, **51**, 159 (1941).

(2) C. Niemann, A. A. Benson and J. F. Mead, THIS JOURNAL, **63**, 2204 (1941).

(3) (a) M. Bergmann and H. Fraenkel-Conrat, *J. Biol. Chem.*, **119**, 707 (1937); (b) C. Niemann and P. L. Nichols, Jr., *ibid.*, **143**, 191 (1942).

(4) Unpublished experiments have shown that the LD_{50} of *o*-fluorophenol in the rat is greater than 100 mg./kg. when administered subcutaneously.

(5) H. E. Carter and C. M. Stevens, *J. Biol. Chem.*, **138**, 628 (1941).

280° with decomposition starting at 265° when heated at the rate of 5°/min.

Anal. Calcd. for $C_9H_{10}O_3NF$ (199): C, 54.3; H, 5.1; N, 7.0. Found: C, 54.3; H, 5.1; N, 6.9: $[\alpha]^{26}D = \frac{0.29 \times 1.95}{1 \times 0.100} = 5.7°$ (in 4% hydrochloric acid).

Toxicity Determinations.—The procedure employed was that described by Phillips, *et al.*,[1a] *i. e.*, single subcutaneous injections of solutions of the hydrochloride in both mature (150–300 g.) and immature (80–150 g.) rats. The toxic symptoms were identical with those reported[1a] and most of the deaths occurred during the first twenty-four hours although the period of observation was taken as forty-eight hours.

TABLE I

TOXICITY DATA

Substance	Moles/kg. × 10⁵[a]	Mortality per group Immature rat	Mature rat
3-Fluoro-*l*(−)-tyrosine	4.5	0/6	
	5.0	0/4	
	6.3	5/10	0/8
	7.5	4/4	4/8
3-Fluoro-*d*(+)-tyrosine	6.3	2/6	0/8
	7.5		4/8
3-Fluoro-*dl*-tyrosine	6.3	2/6	0/8
	7.5		6/8

[a] Mg./kg. = moles/kg. × 2 × 10⁵.

GATES AND CRELLIN LABORATORIES OF CHEMISTRY
CALIFORNIA INSTITUTE OF TECHNOLOGY
PASADENA, CALIF. RECEIVED MAY 20, 1946

Synthesis of 2,4-Dichloropropiophenone

BY JOHN T. SHEEHAN[1]

According to the available literature,[2,3] the Friedel–Crafts condensation of acyl halides with dihalogenated benzene derivatives proceeds with the formation of negligible or vanishing yields. Consequently it seemed worth while to note the present exception to this observed behavior, which was encountered in the course of another investigation. In this instance, the yield was found equal to that obtained in the usual Friedel–Crafts condensation between acyl halides and aromatic hydrocarbons, albeit a longer period of heating and a greater amount of anhydrous aluminum chloride than usual were employed.

Experimental

2,4-Dichloropropiophenone.—Forty grams (0.27 mole) of *m*-dichlorobenzene and 48 g. (0.50 mole) of propionyl chloride were dissolved in 300 cc. of carbon disulfide. The solution was refluxed on a steam-bath while stirring, and to it was added, over a period of ten minutes, 160 g. (1.20 moles) of anhydrous aluminum chloride. The heating and stirring were continued for twenty-four hours, during which time the evolution of hydrogen chloride was noticeable but never vigorous. The carbon disulfide was then distilled off and the residue poured into 300 cc. of 6 *N* hydrochloric acid in ice. The oily layer which separated was extracted with four 125-cc. portions of benzene. The combined benzene extract was washed twice with 300 cc. of water, once with 350 cc. of 10% sodium hydroxide, and finally three times with 300 cc. of water. It was then dried over anhydrous calcium chloride. The latter was filtered off, the solvent evaporated and the residue distilled. The main fraction boiled at 118–120° at 5 mm. On redistillation it boiled at 121–123° at 6.5–7 mm. The yield was 48.5 g. (89%). At 19 mm. the boiling point is 138–140°; $n^{25}D$ 1.5510 and d^{25} 1.2871.

Anal. Calcd. for $C_9H_8OCl_2$: C, 53.20; H, 3.95; Cl, 34.97. Found: C, 53.10; H, 3.89; Cl, 34.96.

On oxidation with potassium permanganate, the above compound yielded only one product, and that in almost quantitative yield. After recrystallization from water it melted at 158°. A mixed melting point with an authentic sample of 2,4-dichlorobenzoic acid gave no depression.

Anal. Calcd. for $C_7H_4O_2Cl_2$: C, 43.97; H, 2.09; Cl, 37.12. Found: C, 44.15; H, 2.30; Cl, 37.09.

WINTHROP CHEMICAL COMPANY, INC.
RENSSELAER, NEW YORK RECEIVED MAY 2, 1946

(1) Present address: Squibb Institute for Medical Research, New Brunswick, N. J.

(2) Thomas, "Anhydrous Aluminum Chloride in Organic Chemistry," A. C. S. Monograph 87, Reinhold Publishing Corp., New York, N. Y., 1941, pp. 226–228.

(3) Roberts and Turner, *J. Chem. Soc.*, 1832 (1927).

Carbonyl Chlorofluoride[1]

BY J. H. SIMONS, D. F. HERMAN AND W. H. PEARLSON

We have found that carbonyl chlorofluoride can be prepared readily by shaking a mixture of hydrogen fluoride and phosgene in a copper bomb at approximately 80° and 280 pounds per square inch pressure. Some fluorophosgene is simultaneously produced but as hydrogen chloride is one of the products and as this boils too close to fluorophosgene for separation by distillation, no significant amounts of fluorophosgene were prepared from these preparations.

The apparatus consisted of a heavy-wall copper bomb of about 250-cc. capacity which was connected to a copper condenser cooled by tap water. The condenser was fitted with a pressure gage and a valve through which the gaseous products could be removed. The bomb was placed in an electrically heated furnace located in a shaking machine. Hydrogen fluoride was removed from the exit gases by means of anhydrous sodium fluoride. After passage through a sulfuric acid bubbler the gases were condensed in traps cooled with liquid air. The procedure consisted of adding to the cooled bomb a charge of about 100 g. of phosgene and 200 g. of hydrogen fluoride. The apparatus was then assembled and heating and shaking begun. When the pressure reached the desired value, between 250 and 300 pounds per square inch, the exit gases were bled off at a rate to maintain the pressure constant. The rate of the reaction was usually negligible below 50° but increased rapidly with temperature so that at 70 to 90° a satisfactory rate of production could be maintained.

Phosgene from different sources gave different rates of production. A sample made by the method of Grignard and Urbain[2] and purified

(1) This paper is based on work done for the Office of Scientific Research and Development under Contract No. NDCrc-167 with Pennsylvania State College.

(2) Grignard and Urbain, *Compt. rend.*, **169**, 17 (1919).

only by bubbling through sulfuric acid gave a satisfactory production of product at 125° with a pressure of 180 pounds per square inch without the use of added catalyst. A sample prepared from carbon monoxide and chlorine, and purified from excess chlorine by amalgamated mossy tin, required a temperature of 145° for an unsatisfactorily slow rate. The addition of 3 cc. of antimony pentachloride increased the rate so that satisfactory production was obtained at 80°.

Distillation of the condensate in the liquid air traps gave a middle fraction of relatively pure carbonyl chlorofluoride, representing about 25% of the initial phosgene. Redistillation of this fraction gave a material with the properties:

Melting point, °C.		−138
Boiling point (760 mm.), °C.		− 42
Vapor pressure to ±5%		log $P_{mm.}$ = 7.93 − (1165/T)
Molecular weight (by vapor density)		82.5
% Chlorine		43.6
Theoretical for COClF	Molecular weight	82.5
	% Chlorine	43.6

The gas has an odor similar to but distinguishable from that of phosgene. It is readily adsorbed by sodium hydroxide or soda lime. It shows no tendency to react with glass. Yields of approximately 50% COClF were obtained in some of the later preparations.

SCHOOL OF CHEMISTRY AND PHYSICS
PENNSYLVANIA STATE COLLEGE
STATE COLLEGE, PA. RECEIVED APRIL 6, 1946

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Unsaturated Alcohol Esters of the 9,10-Dihydroxystearic Acids. Preparation of Elaidyl Alcohol

BY DANIEL SWERN, E. F. JORDAN, JR., AND H. B. KNIGHT

During a recent investigation it was necessary to identify a series of by-products which appeared to be unsaturated alcohol esters of 9,10-dihydroxystearic acid. A search of the literature revealed that none of these compounds had been described previously. To facilitate their identification, we have prepared the allyl, methallyl, β-chloroallyl, furfuryl, cinnamyl, oleyl and elaidyl esters of both 9,10-dihydroxystearic acids, m. p. 95 and 130°, respectively.

Elaidyl alcohol is not a very well-known compound, since its preparation is extremely tedious. It is usually prepared by reduction of purified methyl or ethyl elaidate with metallic sodium and absolute alcohol, and purified by fractional distillation and crystallization.[2] We have worked out a convenient method for its preparation in fair yield from commercial or highly purified oleyl alcohol. Elaidyl alcohol, m. p. 36–37°, is obtained as glistening plates.

Experimental

Materials.—Low melting 9,10-dihydroxystearic acid (m. p. 95°) and its high-melting isomer (m. p. 130°), and their methyl esters (m. p. 70 and 104°, respectively) were prepared as previously described.[3,4] Purified oleyl alcohol was prepared from the commercial grade by low temperature solvent crystallization and fractional distillation.[5] The allyl, methallyl, β-chloroallyl, cinnamyl and furfuryl alcohols were the purest commercial grades and were fractionally distilled before use.

Two alternative procedures were employed for the preparation of elaidyl alcohol.

1. Commercial oleyl alcohol (oleyl alcohol content, 60 to 70%) was distilled through an 18-inch Vigreux column, and the fraction boiling at 165–205° (4.3 mm.), which amounted to about 85% of the starting material, was retained. Six hundred grams was dissolved in 9000 ml. of acetone, and the solution was cooled to −20° to precipitate solid (saturated) alcohols. The liquid alcohols (470 g.), obtained from the filtrate, were heated and stirred for two hours in a nitrogen atmosphere at 220–225° with 0.3% of powdered selenium.[6] The cooled reaction mixture was dissolved in 4700 ml. of acetone, treated with active carbon and filtered, and the filtrate was cooled to −20°. The precipitate, m. p. about 30°, consisted mainly of elaidyl alcohol and weighed 200 g. Pure elaidyl alcohol, m. p., 36–37° (lit. 35–35.5°),[2] was obtained after one additional crystallization from acetone at −20° and two at 0°. The yield was 56 g. *Anal.* Iodine number: Calcd., 94.5; Found, 93.4,

2. Purified oleyl alcohol[5] (270 g., oleyl alcohol content, 97%) was isomerized as described above. Crystallization from acetone at −20°, after treatment of the solution with active carbon, yielded 164 g. of fairly pure elaidyl alcohol m. p. about 33°; iodine number, about 91. Pure elaidyl alcohol, m. p., 36–37°, was obtained after two additional crystallizations from acetone at 0 to −5°. The yield was 110 g. Iodine number was 93.6.

Esterification Procedures.—The allyl, β-chloroallyl, oleyl and elaidyl esters were prepared by direct esterification of the corresponding alcohol with the dihydroxystearic acids, previously reported methods being employed.[3] In these preparations, with the exception of the allyl esters, the azeotropic method was used. Approximately 2–3 ml. of allyl and β-chloroallyl alcohol per gram of acid were employed, as compared with 20% molar excesses of oleyl and elaidyl alcohols. Yields of crude esters were quantitative.

The methallyl, furfuryl and cinnamyl esters were prepared by alcoholysis of methyl 9,10-dihydroxystearate with the appropriate alcohol. A typical preparation is as follows: To 0.5–1.0 mole of the freshly distilled alcohol, 0.4 g. (0.017 mole) of metallic sodium was added slowly at room temperature. When the sodium was completely dissolved, 0.05 mole of methyl 9,10-dihydroxystearate was added, and the mixture was heated on the steam-bath for three hours in a nitrogen atmosphere, with occasional shaking. The methyl alcohol formed in the reaction was permitted to escape. The reaction mixture was poured into a large quantity of hot water, and the aqueous layer was separated and discarded. The product was washed with hot water and cooled to room temperature. The solid product obtained was crystallized to constant melting point from 95% ethyl alcohol (2 to 5 ml./g.).

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Not copyrighted.

(2) Toyama, *Chem. Umschau Fette, Öle, Wachse Harze*, **31**, 13 (1924).

(3) Swern and Jordan, THIS JOURNAL, **67**, 902 (1945).

(4) Swern, Billen, Findley and Scanlan, *ibid.*, **67**, 1786 (1945).

(5) Swern, Knight and Findley, *Oil & Soap*, **21**, 133 (1944).

(6) Bertram, *Chem. Weekblad*, **33**, 3 (1936).

TABLE I

UNSATURATED ALCOHOL ESTERS OF 9,10-DIHYDROXYSTEARIC ACID

Ester	Melting point, 95° Yield,[a] %	M. p., °C.	Sapn. no. Calcd.	Found	Iodine no. Calcd.	Found	Melting point, 130° Yield,[a] %	M. p., °C.	Sapn. no. Calcd.	Found	Iodine no. Calcd.	Found
Allyl	30	59.8–60.7	157.4	158.1	71.2	70.0	46	98.8–99.1	157.4	157.1	71.2	71.4
Methallyl	58	60.5–61.0	151.4	151.9	68.4	68.4	53	92.8–93.3	151.4	151.4	68.4	67.6
β-Chloroallyl[b]	52	67.3–67.7	...	...	..	..	59	98.2–98.4	...	...	..	..[c]
Furfuryl	36	69.9–70.2	141.5	143.0	..	..	51	99.0–99.3	141.5	142.5	..	..
Oleyl	50	52.0–52.4	98.9	101.3	44.8	43.6	67	79.9–80.2	98.9	100.2	44.8	43.8
Elaidyl	53	70.2–70.7	98.9	101.3	44.8	43.9	70	84.7–85.2	98.9	101.0	44.8	44.6
Cinnamyl	42	74.4–74.9	129.7	130.1	..	..	34	101.1–101.4	129.7	131.5	..	..

[a] Purified products, after at least three crystallizations from 95% ethanol. [b] (Low melting point) Calcd.: C, 64.6; H, 10.1. Found: C, 64.8; H, 9.8. (High melting point) Calcd.: C, 64.6; H, 10.1. Found: C, 64.8; H, 9.9. [c] The theoretical iodine number could not be obtained (*cf.* Shriner, "Quantitative Analysis of Organic Compounds, 2nd ed., 1941, p. 51).

Results and Discussion

The results are summarized in Table I. With the exception of the furfuryl ester, which becomes slightly yellow after exposure to light and air, the products are white, crystalline solids. The esters prepared from the low-melting form of 9,10-dihydroxystearic acid are insoluble in water and Skellysolve B, and soluble in 95% ethanol, acetone, toluene, ethyl acetate and nitropropane. The esters prepared from the high-melting form of 9,10-dihydroxystearic acid are also insoluble in water and Skellysolve B, but only slightly soluble at room temperature in the other solvents mentioned. On gentle warming, however, they dissolve readily. Preliminary investigation indicated that some of these compounds may be good plasticizers for ethyl cellulose and cellulose acetate.

PHILADELPHIA 18, PA. RECEIVED MAY 13, 1946

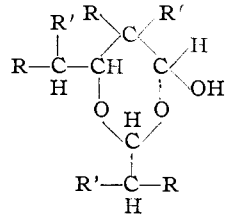
Glycol Esters from Aldehydes

BY FRANK J. VILLANI AND F. F. NORD

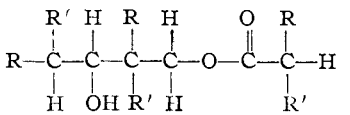
Investigations of several schools which were not fully independent have shown that products of aldehyde condensations lead sometimes to conflicting interpretations of the essential steps involved in their formation. Simple esters, polymers, aldols, glycol esters and 1,3-dioxanes are reported to have been isolated, depending on the nature of the condensing agent used.[1] Raman spectra which might support the contention that a number of isolated glycol esters[2] should be regarded as 1,3-dioxanes failed to do so because the carbonyl line does not appear in, or disappears from, the spectrum. It is also suggested that although the refractive indices and the densities of the glycol esters differ considerably from those of the isomeric 1,3-dioxanes, the corresponding boiling points are very close.

To finally clarify this question we have prepared the dioxanes and the corresponding glycol esters as described in the literature,[2,3] and we have also examined the physical and chemical properties of both.

Both compounds, the 1,3-dioxanes



and the glycol esters



give the same breakdown products on proper treatment with alcoholic alkali.

Accordingly the benzoates[4] were prepared, which resulted in the following observations (Table I).

Experimental.—A representative procedure for the preparation of the glycol esters is as follows:

To a mole of the aldehyde is added a quantity of the coordination catalysts equal to 5% of the weight of the aldehyde. The flask is quickly stoppered and cooled under the tap. After the initial reaction has subsided, the mixture was permitted to stand for twenty-four hours at room temperature. Without further treatment the contents of the flask are fractionated.

The procedure for the preparation of the dioxanes[5] is as follows:

To a mixture of equal volumes of aldehyde and ether, in the presence of a few drops of diethylamine, 10% potassium hydroxide was added dropwise with vigorous stirring, maintaining the temperature at 5–10°. The reaction is complete when the temperature fails to rise on the addition of further alkali. After separation, washing thoroughly

(1) Owen, "Ann. Rep. on the Progress of Chem.," **41**, 139–148 (1945).

(2) Kulpinski and Nord, *J. Org. Chem.*, **8**, 256–270 (1943).

(3) Späth, Lorenz and Freund *Ber.*, **76**, 57 (1943).

(4) Shriner and Fuson, "The Systematic Identification of Organic Compounds," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1945, p. 137.

(5) Saunders, Murray and Cleveland, THIS JOURNAL, **65** (1943).

TABLE I

Aldehyde →			Acetaldehyde		Isobutyraldehyde	
Condensing agent			KOH + Et_2NH	$Mg(Al(C_2H_5)_4)_2$	KOH + Et_2NH	$Mg(Al(OC_4H_9)_4)_2$
Isolated product			2,6-Dimethyl-1,3-dioxane-4-ol	Monoacetate of 1,3-butanediol	2,6-Diisopropyl-5,5-dimethyl-1,3-dioxane-4-ol	Monoisobutyrate of 2,2,4-trimethyl-1,3-pentanediol
B. p.	°C.		68–72	85–89	90–95	103–105
	Mm.		2	11	4	2
$n^{25}D$			1.4380	1.4190	1.4463	1.4390
Benzoate	B. p. °C.		90–100	135–137	104–105	161–163
	B. p. Mm.		2	2	3[b]	1[a]
	M. p., °C.		92–93[a]	....	87–90	....
	$n^{25}D$		....	1.5045	....	1.5575
	d^{25}		....	1.0695	....	1.1200
	Yield, %		47.0	53.2	33.5	45.0
	Analyses, % Carbon	Calcd.	66.10	66.10	71.25	71.25
		Found	66.30	66.26	67.12	72.01
	Analyses, % Hydrogen	Calcd.	6.78	6.78	8.75	8.75
		Found	6.82	6.46	7.52	7.82

[a] A slight decomposition appeared to be unavoidable. The observed molar refraction of 92.26 is in agreement with the calculated value of 92.17. [b] Distilled over as a wax-like solid. This compound was partially solidified and was extremely hygroscopic, and as a result did not give a satisfactory analysis.

with water, drying over anhydrous sodium sulfate, the ethereal solution was finally rectified.

It is obvious from the data recorded that the benzoates prepared are entirely different and that depending on the nature of the catalyst, the products of the condensation are not identical. In the case of the acetaldehyde, we were able to isolate both the dioxane and the glycol ester. However, when the condensation of isobutyraldehyde was performed with our coördination catalyst, we obtained only the glycol ester.

COMMUNICATION NO. 46 FROM
THE DEPARTMENT OF ORGANIC CHEMISTRY
FORDHAM UNIVERSITY, NEW YORK 58, N. Y.

RECEIVED DECEMBER 29, 1945

COMMUNICATIONS TO THE EDITOR

IMPROVED PROCEDURES FOR THE PREPARATION OF SOME ORGANOSILICON COMPOUNDS

Sir:

The general methods used for the synthesis of R_4Si compounds have involved reaction of silicon tetrachloride with dialkylzinc[1] compounds, with RX compounds and sodium,[2] and with Grignard reagents.[3] The Wurtz modification was also used incidentally by Schumb and co-workers[4] to prepare R_4Si compounds from silicon hexachloride, an RX compound and sodium. In addition, tetra-*n*-butylsilane was prepared in 50% yield from ethyl orthosilicate with a 25% excess of *n*-butylmagnesium bromide and extensive heating.[5] These several procedures have given low to moderate yields or have involved relatively drastic conditions.

Incidental to a study of the preparation of some organosilicon compounds containing functional groups, we have examined the use of organolithium compounds. We have observed that silicon tetrachloride or ethyl orthosilicate or ethyl orthothiosilicate in ether react almost immediately with the simple alkyllithium and aryllithium compounds in ether to give excellent yields of R_4Si compounds.

$$SiCl_4 + 4RLi \longrightarrow R_4Si + 4LiCl$$

With silicon tetrachloride and the appropriate RLi compound, the yield of tetraethylsilane was 92%, the yield of tetra-*n*-butylsilane was 98%, and the yield of tetraphenylsilane was 99%. From ethyl orthosilicate the yield of tetra-*n*-butylsilane was 97%, and the yield of tetraphenylsilane was 98%. The yield of tetraphenylsilane from ethyl orthothiosilicate was also 98%. Color

(1) Friedel and Crafts, *Ann.*, **127**, 28 (1863).
(2) Polis, *Ber.*, **18**, 1540 (1885).
(3) Kipping, *J. Chem. Soc.*, **91**, 209 (1907); Dilthey and Eduardoff, *Ber.*, **37**, 1140 (1904).
(4) Schumb, Ackerman and Saffer, THIS JOURNAL, **60**, 2486 (1938).
(5) Post and Hofrichter, *J. Org. Chem.*, **5**, 572 (1940).