benzoic acid titration showed 2.24 double bonds suggesting a resistant double bond.[37] A sample of 195 mg. (0.000527 mole) of the triene was mixed with 200 mg. of previously reduced platinum oxide in 25 cc. of ethyl acetate. On shaking, the mixture rapidly took up 24.1 cc. (S.T.P.) of hydrogen, corresponding to 2.04 double bonds, showing a hindered double bond. The filtered solution was evaporated to dryness. The oily residue was crystallized from acetone–methanol to give 125 mg. of needles, melting point 51–55°. Perbenzoic acid titration showed 1.1 double bonds. The product gave no Tortelli–Jaffe or Rosenheim tests but gave a red Liebermann–Burchard test and absorbed bromine. α-Cholestene melts at 53–54°.[38] The product, presumably α-cholestene, was isomerized as usual with anhydrous hydrogen chloride in chloroform at 0°. The solution was washed neutral, dried and evaporated to dryness, giving a residue which was chromatographed on alumina from hexane. The product was crystallized from acetone–methanol but was not obtained pure, melting point 43–46°, known for β-cholestene, 73–74°.[38] The crude material was reduced catalytically as before and took up hydrogen corresponding to 1.2 double bonds. The crude residue was treated to remove unsaturated material[39] and the resulting product chromatographed from hexane on alumina. Crystallization from benzene and nitro-ethane gave cholestane, m.p. 76–77.5°, $[\alpha]^{23.5}\text{D}$ + 23.2° which showed no depression when mixed with an authentic sample.

Preparation of 3,5-Cholestadiene and Cholestane.—3,5-Cholestadiene was prepared for comparison by the usual method[40] of heating cholesteryl methyl xanthate (m.p. 126–127°) to 200° *in vacuo*. Crystallization from ether and acetone gave needles, melting point 75–77°, with E = 495 at 2350 Å. and secondary peaks at 2275 and 2425 Å.

Cholestane was prepared for comparison by catalytic reduction of 3,5-cholestadiene. The product was chromatographed and crystallized from benzene and nitroethane to give needles, melting point 79–80°, $[\alpha]^{27}\text{D}$ + 25.2°. The properties are given as melting point 79–80°, $[\alpha]\text{D}$ +24.5°, +24.8°.[41]

The Action of *n*-Amylsodium on Sterols.—Cholesterol is recovered quantitatively when subjected to the cleavage reagent. 7-Dehydrocholesterol, however, gave a reaction mixture only 94% precipitable by digitonin, indicating some decomposition. The use of alcohol to decompose the excess reagent gave only a 72% recovery of 7-dehydrocholesterol as indicated by the absorption spectrum. The remaining 22% sterol is probably a sodium and alcohol reduction product, *e.g.*, 7-cholestenol.

Other Cleavage Reagents and Conditions.—*n*-Butylsodium gives somewhat lower yields (30–50% of cholesterol), as does *n*-hexylsodium. Satisfactory results can be obtained with cholesteryl ethers at room temperature, using more reagent, or with low speed stirring. High speed stirring, however, permits shorter reaction periods, lower temperatures and less reagent, causing less decomposition of 7-dehydrosteroids. Unsatisfactory results are found with ethyl and *t*-butyl chlorides or alkyl bromides. Other reagents giving little or no cleavage are sodium, sodium–potassium alloys, potassium, alkyllithiums (less than 10% sterol) and alkylpotassiums or mixtures (tendency to form unsaturated hydrocarbon). The alkali amalgams are useful in preparing the alkylalkalies, but are not necessary. Temperatures below 0° or above 25° are not advisable. Ether, pyridine and methylcyclohexane were tried as solvents, but the most satisfactory results were only obtained with saturated hydrocarbons (b.p. 100° or less).

Acknowledgment.—Grateful acknowledgment is expressed to Mr. A. E. Briod and Dr. Kenneth Morgareidge for their interest and encouragement during the course of this research. Thanks are due for the able technical assistance of Miss Edith Greenfield and Mrs. Grace Barrett. Absorption spectra were performed by Mr. William McGarry.

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[37] The material was extremely sensitive to air oxidation. Storage at −15° in an infrequently opened desiccator filled with CO_2 was not satisfactory. A sample so stored, whose m.p. had lowered to 50–55° was analyzed and as expected had a low carbon value. Found: C, 85.07; H, 11.82. Calcd.: C, 88.44; H, 11.56. There was insufficient material for repurification.

[38] J. C. Eck and E. W. Hollingsworth, THIS JOURNAL, **63**, 2986 (1941).

[39] R. J. Anderson and F. Nabenhauer, *Org. Syntheses*, **17**, 46 (1937).

[40] J. C. Eck, R. L. van Peursem and E. W. Hollingsworth, THIS JOURNAL, **61**, 171 (1939).

[41] H. Sobotka, "The Chemistry of the Sterids," The Williams and Wilkins Co., Baltimore, Md., 1937.

HARRISON, NEW JERSEY RECEIVED AUGUST 16, 1950

[FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, MEDICAL RESEARCH DIVISION, SHARP AND DOHME, INC.]

Syntheses with *cis*-Hexahydrophthalic Anhydride

BY FREDERICK C. NOVELLO AND MARCIA E. CHRISTY

Condensation between *cis*-hexahydrophthalic anhydride and anisole in the Friedel–Crafts reaction yielded three products, *cis*- and *trans*-2-(*p*-anisoyl)-cyclohexane-1-carboxylic acid and 2,2-bis-(*p*-methoxyphenyl)-hexahydrophthalide. *cis*-Hexahydrophthalic anhydride underwent the Perkin reaction but in low yield. Three phenolic estrogens were converted to the corresponding carbinols by high pressure catalytic hydrogenation.

As part of a synthetic program in search of nonsteroidal compounds with hormonal activity, *cis*-hexahydrophthalic anhydride was considered a promising intermediate because of its availability and potential application to the various synthetic methods developed for phthalic anhydride. In the Friedel–Crafts reaction, *cis*-hexahydrophthalic anhydride has been found to react readily with benzene to give 2-benzoylcyclohexane-1-carboxylic acid.[1] The results of further studies are presented in this paper.

Depending upon the conditions selected, the Friedel–Crafts reaction between *cis*-hexahydrophthalic anhydride and anisole could be directed to give any one of three products. Two of these products were *cis*- and *trans*-2-(*p*-anisoyl)-cyclohexane-1-carboxylic acids (I). The low-melting *cis* isomer was obtained when the reaction was conducted in nitrobenzene with equimolar quantities of anhydride and anisole. The *trans* isomer was isolated as an artifact as a result of the lability of the *cis* form in hot aqueous alkali. This isomerization occurred when the alkaline reaction mixture was subjected to steam distillation for removal of nitrobenzene. Assignment of the *cis* configuration to the low-melting acid was based on the following considerations: the anhydride used as starting material is known to have the *cis* configuration; on refluxing with aqueous alkali, the low-melting acid was transformed to the high-melting acid; and, on further treatment with anisole and aluminum chloride, the

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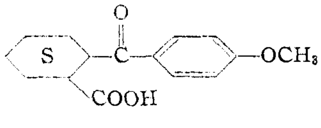
[1] Fieser and Novello, THIS JOURNAL, **64**, 802 (1942).

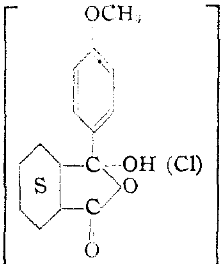
low-melting acid yielded the phthalide, II, whereas, under the same conditions the high-melting isomer was inert. In view of the fact that the formation of diphenyl phthalide from benzoylbenzoic acid and benzene in the presence of excess aluminum chloride is considered to proceed through the hydroxy lactone of 2-benzoylbenzoic acid,[2] a similar transformation of I to II through a cyclic hydroxy (or chloro) lactone (IIa) would be possible only when the keto acid (I) has a *cis* configuration. The formation of phthalide (II) from only the low-melting acid is thus in harmony with a *cis* configuration for this isomer.

The third product, 2,2-bis-(*p*-methoxyphenyl)-hexahydrophthalide (II) that was formed in the Friedel–Crafts reaction between *cis*-hexahydrophthalic anhydride and anisole was obtained only when the anisole was used in excess and without a diluent.

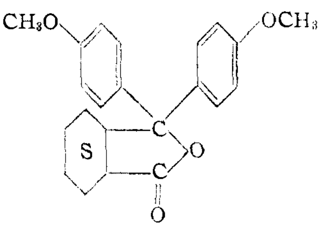
Further experimentation with 2-(*p*-anisoyl)-cyclohexane-1-carboxylic acid was concerned with the syntheses of compounds IV, V and VI. Reduction of I to 2-(*p*-methoxybenzyl)-cyclohexane-1-carboxylic acid (III) was successful only with the *trans* isomer and was accomplished by high pressure hydrogenation over copper chromite catalyst without solvent.[1] Attempted reduction of the *cis* acid, either chemically with zinc and sodium hydroxide or catalytically over copper chromite, resulted in isomerization to the *trans* form. Conversion of III to 2-(*p*-methoxybenzyl)-1-acetoxyacetylcyclohexane (V) and 2-(*p*-methoxybenzyl)-1-chloroacetylcyclohexane (IV) was readily accomplished through the diazoketone synthesis.[3] The chloro compound (IV) upon conversion to the iodomethyl ketone was reduced with zinc and acetic acid[4] to give 2-(*p*-methoxybenzyl)-1-acetylcyclohexane (VI).



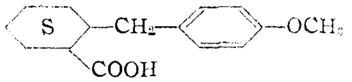
I *cis* and *trans*



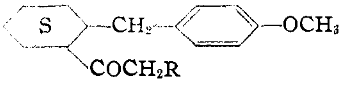
IIa



II

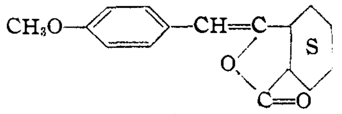


III



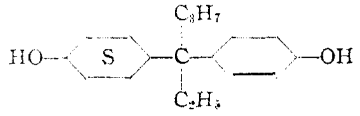
IV R = Cl
V R = OCOCH$_3$
VI R = H

In the Perkin reaction,[5] *cis*-hexahydrophthalic anhydride underwent condensation with *p*-methoxyphenylacetic acid to give *p*-methoxybenzalhexahydrophthalide (VII); under the conditions employed, however, the yield was very low.

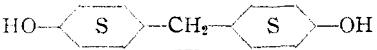


VII

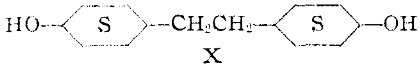
Included in this paper are some experiments on the catalytic hydrogenation of phenolic estrogens to their hydroaromatic analogs as a possible source of synthetic androgens. Such a transformation was demonstrated with estrone and the product obtained, octahydroestrone, was claimed to have androgenic properties.[6] This observation has been confirmed in our laboratories also. High pressure catalytic hydrogenation with either palladium-on-strontium carbonate,[7] or Raney nickel, was utilized to convert 3,3-di-(4-hydroxyphenyl)-hexane, 4,4′-dihydroxydiphenylmethane and 4,4′-dihydroxystilbene[8] to their hydroaromatic analogs, VIII, IX and X, respectively. Separation of the stereoisomers of these carbinols was not investigated. The diketones XI and XII were prepared by oxidation of the corresponding carbinols. None of these compounds demonstrated any significant androgenic activity when evaluated by the chick comb test.[9]



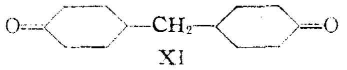
VIII



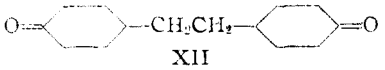
IX



X



XI



XII

Acknowledgment.—The authors wish to express their appreciation to Dr. James M. Sprague for his encouragement and many helpful suggestions during this investigation.

Experimental[10]

2-(*p*-Anisoyl)-cyclohexane-1-carboxylic Acid (I).—A solution of 32 g. (0.21 mole) of *cis*-hexahydrophthalic anhydride[1] and 22.7 g. (0.21 mole) of anisole in 400 cc. of nitrobenzene was treated at 0° with 80 g. (0.6 mole) of aluminum chloride over a 15-minute period. The mixture was stirred in the cold for 2 hours

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[2] (a) von Pechmann, *Ber.*, **33**, 2026 (1900); (b) C. A. Thomas, "Anhydrous Aluminum Chloride in Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1941, p. 516.

[3] "Preparative Organic Chemistry," 1st American Edition, Interscience Publishers, New York, N. Y., 1948, pp. 567–568.

[4] Reichstein and Fuchs, *Helv. Chim. Acta*, **23**, 684 (1940).

[5] Weiss, *Org. Syntheses*, **13**, 10 (1933).

[6] Schwenk and Hildebrandt, *Naturwissenschaften*, **21**, 177, 286 (1933); Schoeller, Schwenk and Hildebrandt, *ibid.*, **21**, 286 (1933).

[7] Martin and Robinson, *J. Chem. Soc.*, 491 (1943).

[8] For the perhydrogenation of diethylstilbestrol, see Ungnade and Ludutsky, *J. Org. Chem.*, **10**, 307 (1945); THIS JOURNAL, **69**, 2629 (1947).

[9] Bioassay experiments were performed by Dr. Ralph Dorfman, Western Reserve University, Cleveland, Ohio.

[10] Microanalyses performed in these laboratories by Mr. K. B. Streeter, Mrs. R. L. Joyce and Mrs. T. P. Buchanan.

and then at 50° for 1.5 hours, cooled and poured onto ice.

trans-**Isomer.**—The mixture was made alkaline with 20% sodium hydroxide and after removal of the nitrobenzene by steam distillation, was cooled, acidified and extracted with ether. The ethereal extract was washed and dried over sodium sulfate. Upon concentration and dilution with petroleum ether, the keto acid was obtained as colorless rhombic rods, m.p. 148–151°. An analytical sample prepared by further recrystallizations from ether–petroleum ether melted at 152.4–153.2°.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92; OCH_3, 11.83. Found: C, 68.91, 68.72; H, 6.82, 6.76; OCH_3, 11.89, 11.69.

cis-**Isomer.**—The mixture was extracted with ether. After extraction of the ethereal solution with 10% sodium hydroxide and subsequent acidification of the alkaline fraction, the product was taken up in ether, washed and dried over sodium sulfate and recrystallized from ether–petroleum ether; yield 35.5 g. (65%) of colorless prisms, m.p. 110–112°. After further recrystallizations from ether–petroleum ether the acid melted at 111.5–113.5°.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.83, 68.73; H, 7.09, 7.10.

Refluxing a solution of 42 g. of the cis isomer with 500 cc. of 10% sodium hydroxide for three hours gave 36.5 g. of the *trans* isomer melting at 151–153°.

2,2-Bis-(*p*-Methoxyphenyl)-hexahydrophthalide (II) (a).—To a cold (0°) stirred solution of 4.6 g. (0.03 mole) of *cis*-hexahydrophthalic anhydride in 30 cc. of anisole, 12 g. of aluminum chloride was added over a 5-minute period. The mixture was stirred at 0° for 10 minutes, then at room temperature for 45 minutes and finally at steam-bath temperature for 10 minutes. After decomposition with ice and hydrochloric acid and extraction with ether, the product was extracted from the ethereal extract with 10% sodium hydroxide. Acidification of the alkaline fraction yielded a gummy solid which crystallized from ether–petroleum ether as colorless needles, m.p. 147–151°; yield 6.4 g. (60%). Further crystallizations raised the melting point to 156–156.7°.

Anal. Calcd. for $C_{22}H_{24}O_4$: C, 74.98; H, 6.86; OCH_3, 17.61. Found: C, 75.03, 75.11; H, 7.11, 7.09; OCH_3, 17.73, 17.77.

(b)—A solution of 5.25 g. (0.02 mole) of *cis*-2-(*p*-anisoyl)-cyclohexane-1-carboxylic acid in 25 cc. of anisole was treated at room temperature with 8.0 g. (0.06 mole) of aluminum chloride. After heating for one hour on the steam-bath, the mixture was cooled, decomposed and processed in the same manner as described in (a); yield 1.8 g. of colorless needles, m.p. 149–152°. Recrystallization gave material melting at 154–157° which showed no depression in melting point on admixture with a sample prepared directly from hexahydrophthalic anhydride.

2-(*p*-Methoxybenzyl)-cyclohexane-1-carboxylic Acid (III).—A mixture of 15 g. of *trans*-2-(*p*-anisoyl)-cyclohexane-1-carboxylic acid and one gram of copper chromite catalyst (37KAF)[11] in a glass liner was shaken with hydrogen at an initial pressure of 1700 lb. at 170° for 3 hours. The resulting black gummy solid was boiled with 350 cc. of 10% soda solution, filtered and acidified. Crystallization of the colorless gum thus obtained from ether–petroleum ether yielded 12.2 g. (86%) of colorless prisms, m.p. 98–101°. An analytical sample melted at 101.3–102.1°.

Anal.[12] Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12; OCH_3, 12.49. Found: C, 72.64, 72.56; H, 8.28, 8.11; OCH_3, 12.69, 12.83.

2-(*p*-Methoxybenzyl)-1-chloroacetylcyclohexane (IV).—Following the procedure of Wilds and Beck,[13] a solution of 3.7 g. (0.015 mole) of 2-(*p*-methoxybenzyl)-cyclohexane-1-carboxylic acid in 30 cc. of dry benzene containing one drop of pyridine was treated with 6 cc. of purified thionyl chloride.[14] After 40 minutes at room temperature the mixture was warmed at 50° for 5 minutes and concentrated to dryness *in vacuo*. A small volume of dry benzene was added and the solution again concentrated to dryness *in vacuo*. This treatment was repeated and the crude acid chloride, dried briefly *in vacuo* at 100°, was dissolved in 25 cc. of absolute ether, cooled in ice and then added to a cold solution of diazomethane in 90 cc. of ether prepared from 6 g. of nitrosomethylurea.[15] After 1 hour at room temperature when gas evolution had ceased, the solution was concentrated to dryness at room temperature and the crude diazoketone was dissolved in 30 cc. of absolute ether, cooled in ice and treated with dry hydrogen chloride. When the vigorous evolution of nitrogen had ceased (3 minutes) the solution was concentrated to dryness *in vacuo* and the residue crystallized from ether–petroleum ether; yield 3.6 g. (86%), pale yellow needles, m.p. 38–43°. Further crystallizations from ether–petroleum ether gave colorless silken needles, m.p. 47.6–49.4°.

Anal. Calcd. for $C_{16}H_{21}O_2Cl$: C, 68.44; H, 7.54; Cl, 12.63. Found: C, 68.64, 68.48; H, 7.26, 7.30; Cl, 12.52, 12.43.

2-(*p*-Methoxybenzyl)-1-acetoxyacetylcyclohexane (V).—The crude diazo ketone prepared from 2.48 g. (0.01 mole) of 2-(*p*-methoxybenzyl)-cyclohexane-1-carboxylic acid was warmed on the steam-bath with 7 cc. of glacial acetic acid for 1.5 hours. The cooled solution was taken up in ether, washed with water and 10% soda solution and dried over sodium sulfate. The product was obtained as yellow needles from ether–petroleum ether; yield 2.25 g. (74%), m.p. 83–86°. The ketol acetate reduced Fehling solution readily and when fully purified melted at 92.5–93.5°.

Anal.[12] Calcd. for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 70.98, 71.09; H, 8.16, 8.28.

2-(*p*-Methoxybenzyl)-1-acetylcyclohexane (VI).—Three grams (0.01 mole) of 2-(*p*-methoxybenzyl)-1-chloroacetylcyclohexane was dissolved in a solution of 1.8 g. of sodium iodide in 50 cc. of acetone and warmed on the steam-bath for 5 minutes. Without filtering the solution from precipitated sodium chloride, the solvent was removed *in vacuo* and the residual unstable iodo compound dissolved in 25 cc. of glacial acetic acid and treated with sufficient zinc dust to make the solution colorless. After warming on the steam-bath for a few minutes, the solvent was removed *in vacuo* and the residue treated with water and extracted with ether. The washed and dried ethereal extract was concentrated to dryness and the residue distilled *in vacuo;* yield 2.5 g. (95%) of colorless mobile oil, b.p. 144° (0.6 mm.).

Anal. Calcd. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.83, 77.83; H, 8.73, 8.97.

***p*-Methoxybenzalhexahydrophthalide (VII).**—A mixture of 4.3 g. of *cis*-hexahydrophthalic anhydride (0.028 mole), 5.64 g. (0.034 mole) of *p*-methoxyphenylacetic acid[16] and 0.12 g. (0.0014 mole) of freshly fused sodium acetate was heated in a sand-bath at 230° for 3 hours. The dark red resin-like gum was taken up in alcohol, treated with decolorizing carbon and after removal of solvent, distilled *in vacuo* at 0.5 mm. The first fraction, 2.7 g., collected at 80–132°, was *p*-methoxyphenylacetic acid. A second fraction, b.p. 135–165°, being a mixture of solid and oil was taken up in ether, washed with soda, dried and redistilled *in vacuo* to give 800 mg. of highly viscous amber colored oil, b.p. 173–178° (0.5–1 mm.).

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.48, 74.38; H, 7.22, 7.08.

3,3-Di-(4-hydroxycyclohexyl)-hexane (VIII).—Three grams of 3,3-di-(4-hydroxyphenyl)-hexane[17] was hydrogenated in 15 cc. of ethanol with 1 g. of Raney nickel at 210° and 1700 lb. pressure for 12 hours. On cooling, the mixture was filtered, concentrated to dryness *in vacuo* and the residue refluxed for 8 hours with 0.5 g. of sodium methoxide in 25 cc. of methanol. After dilution with water, the product was extracted with ether which was washed, dried and concentrated to dryness. Distillation of the residue gave 1.65 g. of colorless glass, b.p. 177–181° (1 mm.).

Anal. Calcd. for $C_{18}H_{34}O_2$: C, 76.54; H, 12.13. Found: C, 76.92, 76.89; H, 11.65, 11.59.

A dibenzoate was obtained which crystallized as colorless glistening flakes, m.p. 110–111.5°.

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(11) Folkers and Connor, THIS JOURNAL, **54**, 1138 (1932).

(12) Microanalyses by Dr. Carl Tiedcke, New York, N. Y.

(13) Wilds and Beck, THIS JOURNAL, **66**, 1692 (1944).

(14) Fieser, "Experiments in Organic Chemistry," 2nd Edition, D. C. Heath and Company, Boston, Mass., 1941, p. 381.

(15) Bachman and Struve in "Org. Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 50.

(16) Kindler and Peschke, *Arch. Pharm.*, **271**, 435 (1933).

(17) Campbell, *Proc. Roy. Soc.* (*London*), **B129**, 528 (1940).

Anal. Calcd. for $C_{32}H_{42}O_4$: C, 78.33; H, 8.63. Found: C, 78.21, 78.45; H, 8.44, 8.47.

Di-(4-hydroxycyclohexyl)-methane (IX).—4,4'-Dihydroxydiphenylmethane was prepared in 64% yield by Clemmensen reduction of 4,4'-dihydroxybenzophenone.[18] Ten grams was hydrogenated in 30 cc. of purified dioxane with 4 g. of 2% palladium-on-strontium carbonate for 4 hours at 165° and 1600 lb. initial pressure. The product was obtained by distillation *in vacuo* as a colorless oil which solidified on standing; yield 7.8 g. (74%), m.p. 94–95°. Crystallization from ethyl acetate gave small needles, m.p. 113.5–114.5°, cloudy melt becoming clear at 119.5°.

Anal.[12] Calcd. for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.80, 73.62; H, 11.35, 11.24.

A dibenzoate was obtained as glistening colorless sheathes from ether–methanol, m.p. 129.5–130°.

Anal.[12] Calcd. for $C_{27}H_{32}O_4$: C, 78.91; H, 7.67. Found: C, 79.06, 79.29; H, 8.08, 8.29.

α,β-Di-(4-Hydroxycyclohexyl)-ethane (X).—Five grams of 4,4'-dihydroxystilbene,[19] 20 cc. of ethanol and 2 g. of Raney nickel in a glass liner were shaken with hydrogen, initial pressure 2000 lb. at 170–180° for 2 hours. A quantitative yield of crystalline product was obtained, m.p. 134.5–139°. Further recrystallization from ethyl acetate gave colorless needles, m.p. 142.5–143.3°, clear melt at 148.5°.

Anal. Calcd. for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58. Found: C, 74.42, 74.21; H, 11.71, 11.63.

A dibenzoate was obtained as colorless needles from ethanol, m.p. 177.3–178.8°.

Anal.[12] Calcd. for $C_{28}H_{34}O_4$: C, 77.39; H, 7.89. Found: C, 77.19, 77.28; H, 8.16, 8.02.

Di-(4-ketocyclohexyl)-methane (XI).—A cold solution of 2.1 g. of di-(4-hydroxycyclohexyl)-methane in 50 cc. of glacial acetic acid was treated with a cold solution of 2.2 g. of chromic acid in 10 cc. of water and 40 cc. of glacial acetic acid. After 18 hours at room temperature, the solution was concentrated to dryness *in vacuo* and the residue diluted with water and extracted with ether. The washed and dried ethereal solution was concentrated and the product crystallized from benzene–hexane; yield 1.25 g. (63%) colorless prismatic needles, m.p. 92.5–94°. Further purification gave colorless leaflets, m.p. 96–96.8°.

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.97, 75.27; H, 9.83, 9.82.

A dioxime was obtained as colorless glistening needles from alcohol–water, m.p. 204–205.5° with previous darkening.

Anal. Calcd. for $C_{13}H_{22}O_2N_2$: C, 65.51; H, 9.31. Found: C, 65.43, 65.21; H, 9.53, 9.30.

α,β-Di-(4-ketocyclohexyl)-ethane (XII) was obtained by chromic acid oxidation of α,β-di-(4-hydroxycyclohexyl)-ethane (2.2 g.) according to the previously described procedure; yield 1.1 g. (50%), colorless flakes, m.p. 95–96.1°.

Anal.[12] Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.98. Found: C, 75.01, 75.30; H, 9.98, 9.90.

A dioxime crystallized from alcohol–water in colorless needles, m.p. 212.5–214.5°.

Anal.[12] Calcd. for $C_{14}H_{24}O_2N_2$: C, 66.63: H, 9.59. Found: C, 66.96, 67.12; H, 9.80, 9.89.

GLENOLDEN, PENNA. RECEIVED SEPTEMBER 5. 1950

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[18] Available from the Dow Chemical Co., Midland, Michigan.

[19] Elbs, *J. prakt. Chem.*, [2] **47**, 60 (1893).

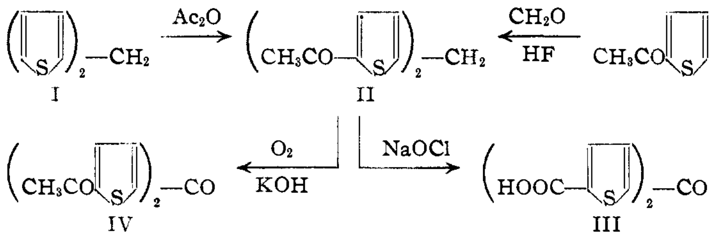
[CONTRIBUTION NO. 281 FROM THE CHEMICAL DEPARTMENT, EXPERIMENTAL STATION, WILMINGTON, DELAWARE, AND CONTRIBUTION NO. 95 FROM THE JACKSON LABORATORY OF THE ORGANIC CHEMICALS DEPARTMENT, DEEPWATER, NEW JERSEY, OF E. I. DU PONT DE NEMOURS & COMPANY]

The Synthesis and Oxidation of 2,2'-Methylene-bis-(5-acetylthiophene)

BY T. L. CAIRNS, B. C. McKUSICK AND V. WEINMAYR

The preparation of 2,2'-methylene-bis-(5-acetylthiophene) and its oxidation have been studied. Sodium hypochlorite gave 2,2'-carbonyl-bis-(5-thiophenecarboxylic acid) (III) while chromic anhydride or oxygen and alkali gave 2,2'-carbonyl-bis-(5-acetylthiophene) (IV). A new method for forming di-2-thienylmethanes from thiophenes and aldehydes, employing 48% hydrofluoric acid as condensing agent, has been developed.

In connection with work on dicarboxylic acids, it became of interest to prepare a dicarboxylic acid containing thiophene nuclei. Accordingly, di-2-thienylmethane (I) was condensed with acetic anhydride in order to form the diketone (II), which was then oxidized with sodium hypochlorite. The product of this oxidation was found to be a keto dicarboxylic acid (III) rather than the expected methylene dicarboxylic acid.



Subsequent study of the literature showed that this oxidation of a methylene group by hypohalite is not unique, for several cases are known in which a methylene group attached to an aromatic ring containing an acyl group is attacked by hypohalite.[1–3]

The observation that the methylene group of II is attacked by hypochlorite prompted a study of the action of other oxidizing agents on II. It was found that either chromic anhydride in hot acetic acid or oxygen at 25° in the presence of dilute alcoholic potassium hydroxide attacked only the methylene group of II to give a high yield of the triketone, IV. The function of the alkali in the latter oxidation probably was removal of a proton from the methylene group to give an easily oxidized anion. Such an anion, as the resonance hybrid of structures such as V and VI, might be expected to have

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[1] Duval. *Bull. soc. chim.*, [4] **7**, 796 (1910).

[2] Schiessler and Eldred. THIS JOURNAL, **70**, 3958 (1948).

[3] It is probable that oxidation of the methylene group preceded transformation of the acetyl groups to carboxyl groups, but this was not proved. Di-2-thienylmethane was recovered unchanged when treated with sodium hypochlorite, which shows that one activating group or more must be present in the thiophene rings if the methylene group is to be attacked by hypohalite.