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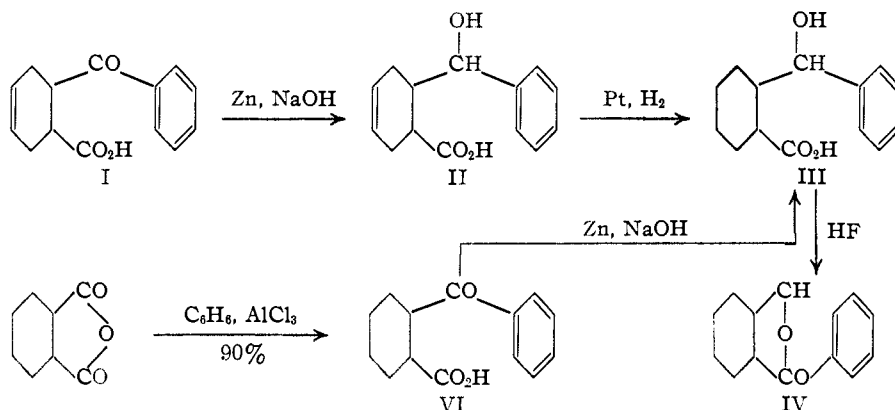
A Synthesis of 4,10-Ace-1,2-benzanthracene Utilizing Δ^4 -Tetrahydrophthalic Anhydride

BY LOUIS F. FIESER AND FREDERICK C. NOVELLO

The conversion of phthalic anhydride into *o*-aroylbenzoic acids, either by a Friedel and Crafts reaction with an aromatic hydrocarbon or by condensation with an aryl Grignard reagent, has provided a very useful point of departure for the synthesis of anthraquinones, 1,2-benzanthraquinones, and the corresponding hydrocarbons. Elaborations of the general "phthalic anhydride" scheme of synthesis have been of particular service in the preparation of *meso*-alkylated 1,2-benzanthracenes of importance in the study of hydrocarbon carcinogenesis. In this investigation we have explored the possibility of utilizing to advantage in specific instances the tetra- or hexahydro derivatives of phthalic anhydride in place of the fully aromatic compound.

Δ^4 -Tetrahydrophthalic anhydride is obtainable from butadiene and maleic anhydride¹ in 90% yield and can be converted by hydrogenation into *cis*-hexahydrophthalic anhydride² in 90% yield. The condensation of aryl Grignard reagents with phthalic anhydride, as first reported by Weizmann and Pickles,³ generally proceeds more satisfactorily than the condensation of the same reagents with succinic anhydride according to Komppa and Rohrmann.⁴ The hydrophthalic anhydrides, however, are more nearly analogous in structure to α,β -dimethylsuccinic anhydride⁵ and cyclopentane-1,2-dicarboxylic anhydride,⁶ which have been found to give somewhat better results in Grignard condensation than the unsubstituted compound. In orienting experiments, Δ^4 -tetrahydrophthalic anhydride was found to

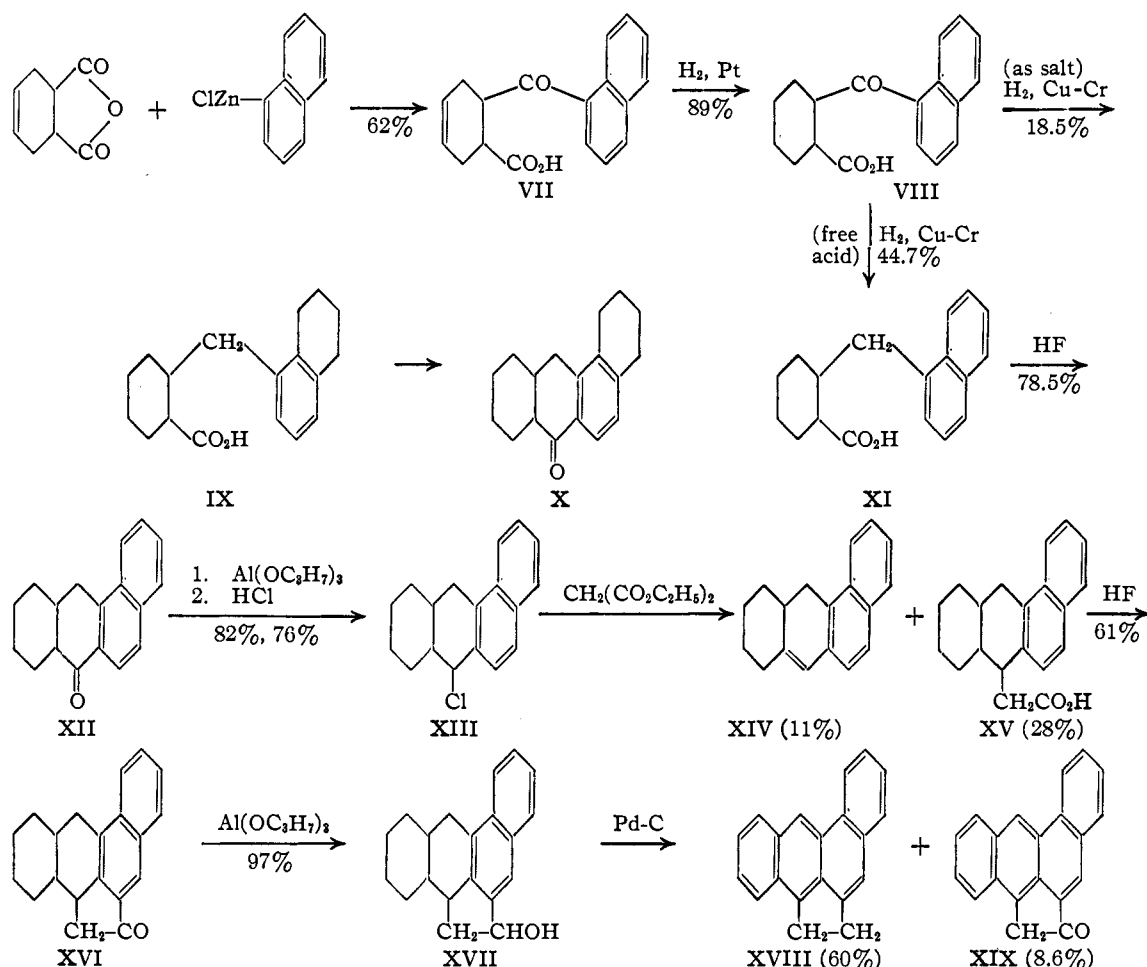
react with phenylmagnesium bromide or phenylzinc chloride to give the unsaturated keto acid I in 37–38% yield. On reduction with zinc and alkali, the keto acid afforded a hydroxy acid (II) of somewhat unusual stability, for it showed little tendency to lactonize in the course of crystallization or on hydrogenation to the saturated hydroxy acid III. Acid treatment of the latter substance, however, gave the lactone IV. As expected, the unsaturated anhydride gave unpromising results in the Friedel and Crafts condensation. *cis*-Hexahydrophthalic anhydride, however, reacted very smoothly with benzene in the presence of aluminum chloride to give 2-benzoylcyclohexane-1-carboxylic acid (VI), and this on reduction with zinc and alkali was converted into the hydroxy acid III.



Although the above compounds offer possibilities for other synthetic operations, the further experimentation of the present work was confined to a second series directed to the synthesis of carcinogenic derivatives of 1,2-benzanthracene, particularly the 4,10-ace-compound XVIII. The keto acid VII was obtained in only 41% yield by the condensation of Δ^4 -tetrahydrophthalic anhydride with α -naphthylmagnesium bromide, but better results were obtained with the use of the corresponding arylzinc chloride, following the procedure found by Tarbell⁷ most satisfactory for the mono-arylation of dimethylmaleic anhydride. Trial experiments with the keto acid VII were

(1) Diels and Alder, *Ann.*, **460**, 98 (1928).
 (2) v. Bayer, *ibid.*, **258**, 219 (1890).
 (3) Weizmann and Pickles, *Proc. Roy. Soc. (London)*, **20**, 201 (1904).
 (4) Komppa and Rohrmann, *Ann.*, **509**, 259 (1934).
 (5) Fieser and Daudt, *THIS JOURNAL*, **63**, 782 (1941).
 (6) E. Bergmann and Blum-Bergmann, *ibid.*, **59**, 1572 (1937).

(7) Tarbell, *ibid.*, **60**, 215 (1938); **62**, 2747 (1940).



made to see whether a methyl group could be introduced at the site corresponding to the 9-position of the ultimate 1,2-benzanthracene, but the best yield of methylated lactone obtained from the ester of VII and methylmagnesium bromide was only 16% and the experimentation in this direction was therefore discontinued.

The unsaturated keto acid VII was then hydrogenated at low pressure and the reduction of the carbonyl group of VIII was attempted. Hydrogenation of the acid over copper chromite catalyst in a slightly alkaline aqueous solution of the sodium salt⁸ gave, in low yield as the only crystalline product isolated, a substance identified as 2-(α -tetralylmethyl)-cyclohexane-1-carboxylic acid (IX) by cyclization with hydrogen fluoride to the ketone X and conversion of this substance by zinc dust distillation into 1,2-benzanthracene. A similar over-hydrogenation was observed by Fieser and Hershberg⁹ in the high-pressure reduc-

tion of 2-(α -naphthyl)-benzoic acid in the absence of solvent, but has not been encountered before in reactions conducted in aqueous solution. In the present case, lowering the temperature and shortening the reaction period resulted merely in a lower yield of the over-hydrogenated acid IX. A number of other methods of reducing the saturated keto acid VIII were tried, but for the most part these either failed completely or gave the desired product in only very low yield. In the best instances, Clemmensen reduction afforded XI in only 9–10% yield, and the acid was sometimes accompanied by the decarboxylation product α -naphthylmethylcyclohexane. Finally, a reasonably satisfactory method was found in hydrogenation over copper chromite without solvent at moderate temperature and pressure,¹⁰ and in this way an adequate amount of the intermediate can be secured. It may be noted that on one occasion the condensation of the tetrahydrophthalic anhydride with α -naphthylzinc chloride

(8) Fieser and Heymann, *THIS JOURNAL*, **63**, 2333 (1941).

(9) Fieser and Hershberg, *ibid.*, **59**, 2331 (1937); **60**, 940 (1938).

(10) Fieser and Hershberg, *ibid.*, **59**, 1023 (1937).

gave a mixture from which there was isolated a small amount of an acid which appears to be a diastereomer of VII. This on hydrogenation over Adams catalyst yielded an acid isomeric with VIII and in which the original configuration thus seems to be retained. When the diastereomer of VIII was hydrogenated at high pressure, however, the product was identical with the 2-(α -naphthylmethyl)-cyclohexane-1-carboxylic acid (XI) obtained from VIII, and it is concluded that epimerization occurs at the high temperature of this catalytic reaction.

Cyclization of XI to the octahydro-1,2-benz-10-anthrone (XII) proceeded smoothly with the use of hydrogen fluoride, and this ketone was utilized as the starting point for building on an ac-bridge extending from the 10- to the 4-position. Such an operation would hardly be feasible with the fully aromatic 1,2-benz-10-anthrone itself because of the marked tendency of the substance to enolize.¹⁰ Thus the advantage of the synthesis proceeding from a hydrophthalic anhydride is that the intermediate cyclic ketone is completely stable in the ketonic form. The Reformatsky reaction proved unpromising in preliminary trials, for although an unsaturated acetic acid derivative was isolated after saponification, the yield was very low. A better method was that employed successfully by Bachmann in a number of instances, for example in his synthesis of cholanthrene.¹¹ The ketone XII was reduced satisfactorily to the corresponding carbinol by the Meerwein-Pon-

dorf reaction using a mixture of isopropyl alcohol and toluene, and the yield was lower when benzene was employed. The chloride XIII was obtained readily with the use of hydrogen chloride and converted by the malonic ester synthesis into the octahydro-1,2-benzanthracene-10-acetic acid (XV). The yield in this step was low, and a significant amount of the chloride was found to have suffered elimination of hydrogen chloride with the formation of the hexahydro-1,2-benzanthracene (XIV); this hydrocarbon on hydrogenation over Adams catalyst afforded the octahydride. An analogous by-product was encountered by Bachmann and Carmack.¹²

The acetic acid derivative XV can undergo ring-closure in only one direction, but brief treatment with hydrogen fluoride gave, in addition to the expected ketone XVI, an acidic product which appears to be a stereoisomer of the starting material XV and which on cyclization by more prolonged treatment with hydrogen fluoride yielded a ketone isomeric with XVI. The Meerwein-Ponndorf reduction of the ketone XVI proceeded smoothly, and in the final step of the synthesis the resulting carbinol XVII was dehydrogenated by Linstead's method¹³ with palladium charcoal in boiling α -methylnaphthalene solution, using the CO₂-flushed boiler of Heymann.¹⁴ The reaction proceeded smoothly and gave a readily separated mixture of a hydrocarbon and a much less soluble ketone. The analysis of the latter substance indicates that it is the aromatized dehydro derivative of the carbinol and has the formula XIX. The hydrocarbon was readily purified and melted constantly at 144.6–146°; the picrate melted at 154.6–156°. The analyses indicate that the hydrocarbon is the expected 4,10-ace-1,2-benzanthracene (XVIII), and the absorption spectrum, kindly determined by Dr. R. N. Jones in ethanol solution (Fig. 1), is entirely typical of an alkylated 1,2-benzanthracene over the range 2300–3200 Å. The bathochromic shift compared with 1,2-benzanthracene is about the same as that of cholanthrene,¹⁵ but more fine structure is present in the region of longer wave length than noted with either the parent hydrocarbon or cholanthrene. An increase in resolution to a fine

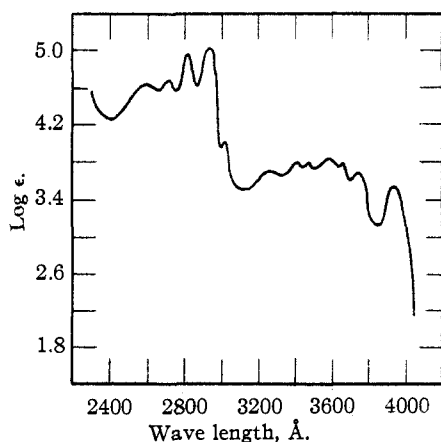


Fig. 1.—4,10-Dimethylene-1,2-benzanthracene in ethanol: absorption maxima (Å.) and log ϵ values: 2592 (4.63), 2710 (4.67), 2815 (4.94), 2935 (5.03), 3025 (4.01), 3270 (3.69), 3415 (3.80), 3475 (3.80), 3575 (3.84), 3665 (3.80), 3745 (3.70), 3935 (3.56).

(11) Bachmann, *J. Org. Chem.*, **8**, 434 (1938).

(12) Bachmann and Carmack, *THIS JOURNAL*, **63**, 1685 (1941).

(13) Linstead and Michaelis, *J. Chem. Soc.*, 1134 (1940).

(14) Fieser and Heymann, *THIS JOURNAL*, **63**, 2338 (1941); Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Co., Boston, Mass., 1941, pp. 461-462.

(15) Mayneord and Roe, *Proc. Roy. Soc. (London)*, **A158**, 634 (1937).

structure attending the introduction of an alicyclic bridge linkage has been observed previously in the case of 1',9-methylene-1,2-benzanthracene,¹⁶ 10-methyl-1',9-methylene-1,2-benzanthracene,¹⁷ and 4,5-methylenechrysene.¹⁸

4,10-Ace-1,2-benzanthracene was synthesized by Fieser and Seligman¹⁹ by the pyrolysis of 1-benzoyl-2,3-cyclopentenonaphthalene and obtained in the form of material melting at 138.5–140° and giving a picrate, m. p. 148–149°. Dansi²⁰ synthesized the hydrocarbon in 1.7% over-all yield by the condensation of 1,2-benzanthracene with oxalyl chloride and zinc dust distillation of the diketone; his material melted at 130°. The hydrocarbon prepared by the present method gave no depression when mixed with the material of Fieser and Seligman. From the melting points, it appears that the new material is somewhat purer than the samples obtained by the two previous syntheses. Since the earlier samples have been found to possess rather high carcinogenic potency at very low dosage levels,^{21,22} the present sample is being assayed by Drs. Shields Warren and C. E. Dunlap.²³

Experimental Part²⁴

1. Condensation of Hydrophthalic Anhydrides with Benzene Derivatives

2-Benzoyl- Δ^4 -cyclohexene-1-carboxylic Acid (I).—In experiments conducted as described in detail in Series 2, the condensation of Δ^4 -tetrahydrophthalic anhydride with phenylmagnesium bromide in ether–benzene afforded the keto acid (m. p. 128–130°) in 38% yield, while with phenylzinc chloride yields of 19–22% were obtained. When a solution of phenylmagnesium bromide in ether–benzene was added slowly with stirring to a solution of the anhydride and zinc chloride in ether–benzene the yield of satisfactory keto acid was 37%. When fully purified by crystallization from ether–petroleum ether, the acid formed colorless needles, m. p. 129.6–131.2°.

*Anal.*²⁵ Calcd. for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 73.33; H, 6.01.

In one experiment the reaction mixture from 5 g. of the anhydride and phenylmagnesium bromide afforded after extensive fractionation 80 mg. of an isomeric keto acid which separated from ether–petroleum ether in transparent, rhombic prisms, m. p. 146–147°; a mixture of this substance with I melted at 108–130°.

(16) R. N. Jones, *THIS JOURNAL*, **62**, 148 (1940).

(17) R. N. Jones, *ibid.*, **63**, 151 (1941).

(18) R. N. Jones, *ibid.*, **63**, 313 (1941).

(19) Fieser and Seligman, *ibid.*, **69**, 883 (1937).

(20) Dansi, *Gazz. chim. ital.*, **67**, 85 (1937).

(21) Morelli and Dansi, *Biochimica e terap. sper.*, **24**, 3 (1937).

(22) Shear, *Am. J. Cancer*, **33**, 499 (1938).

(23) With the assistance of a grant from the Jane Coffin Childs Fund for Medical Research.

(24) All melting points are corrected.

(25) Microanalysis by Eleanor Werbie.

Anal. Calcd. for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 73.38; H, 6.42.

2-(α -Hydroxybenzyl)- Δ^4 -cyclohexene-1-carboxylic Acid (II).—A mixture of 3 g. of the keto acid I, 10 g. of zinc dust, 15 g. of sodium hydroxide, and 150 cc. of water was refluxed for six and one-half hours, cooled, acidified without filtration, and extracted with ether. The washed solution on extraction with soda solution yielded an oil which crystallized from ether–petroleum ether to give 1.57 g. (56%) of colorless, prismatic needles, m. p. 149–151°, dec. On further purification the acid formed transparent prisms, m. p. 154–155.8°, dec.

*Anal.*²⁵ Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.95. Found: C, 72.70; H, 6.71.

2-(α -Hydroxybenzyl)-cyclohexane-1-carboxylic Acid (III).—Hydrogenation of the unsaturated acid II proceeded rapidly in absolute ethanol in the presence of Adams catalyst and afforded the saturated acid, m. p. 150–152°, dec., in 83.5% yield. After three recrystallizations from ether–petroleum ether the product was obtained as colorless, prismatic needles, m. p. 156.3–157.0°, dec. Mixtures of this substance with the unsaturated acid showed but little depression; thus a mixture with 10 parts of II melted at 153.5–154°, dec.

*Anal.*²⁵ Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.75. Found: C, 72.13; H, 7.95.

α -Phenylhexahydrophthalide (IV).—Treatment of the saturated acid III with hydrogen fluoride for two minutes and crystallization of the neutral fraction of the reaction mixture from alcohol gave in 79% yield a mixture of prisms and needles melting at 79–85°. Recrystallization gave colorless needles, m. p. 80–88°, which on standing in contact with the mother liquor changed into prisms, m. p. 86.8–88.4°. The ketone dissolves slowly when boiled with aqueous alkali.

*Anal.*²⁵ Calcd. for $C_{14}H_{16}O_2$: C, 77.74; H, 7.46. Found: C, 78.08; H, 7.82.

2-Benzoylcyclohexane-1-carboxylic Acid (VI).—The required *cis*-hexahydrophthalic anhydride was prepared conveniently by hydrogenation of Δ^4 -tetrahydrophthalic anhydride (5 g.) in purified ethyl acetate (70 cc.) using Adams catalyst (750 mg.). Shaking was stopped at the 1-mole stage (fifteen minutes) and the product was obtained as a colorless oil, b. p. 148–150° (12–13 mm.), which crystallized on standing overnight at -10° to a solid, m. p. 31–32° (Baeyer,² 31–32°); yield 4.57 g. (90%).

A solution of 5.5 g. of *cis*-hexahydrophthalic anhydride in 65 cc. of pure benzene was stirred in ice and 10.7 g. of aluminum chloride was added in the course of five minutes. The yellow mixture was stirred without further cooling for forty minutes and then warmed on the steam-bath for twenty minutes. After decomposition with acid in the cold, the benzene layer was extracted with 5% soda solution. Acidification gave a white crude product which crystallized from ether in colorless prisms, m. p. 138–140°; yield 7.45 g. (90%). An analytical sample melted at 138.6–140°.

*Anal.*²⁵ Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.70, 72.60; H, 7.20, 7.29.

Reduction of the keto acid (3 g.) was accomplished with zinc dust and boiling aqueous alkali exactly as described

for the preparation of the unsaturated hydroxy acid II. Crystallization of the soda-soluble fraction from ether-petroleum ether gave 1.9 g. (63%) of 2-(α -hydroxybenzyl)-cyclohexane-1-carboxylic acid as colorless prisms, m. p. 145–147°, dec. On further purification the acid melted at 155–156°, dec., and gave no depression when mixed with the sample prepared by the method described above.

2. Synthesis of 4,10-Ace-1,2-benzanthracene

2-(α -Naphthoyl)- Δ^4 -cyclohexene-1-carboxylic Acid (VII).—In the preparation of the required Δ^4 -tetrahydrophthalic anhydride¹ a mixture of 50 g. of maleic anhydride and 80 cc. of benzene in a soda bottle was chilled at 0°, and the bottle was tared, charged with 32 g. of butadiene by distillation, capped, and placed in an autoclave along with 100 cc. of benzene. The reaction mixture was allowed to stand at room temperature for twelve hours and then heated at 100° for five hours. Crystallization of the product from benzene-ligroin yielded 69.9 g. (90%) of long, colorless needles, m. p. 101–103°.

A solution of 20.8 g. of freshly fused zinc chloride in 100 cc. of dry ether was added slowly to a stirred ether-benzene solution of the Grignard reagent from 31.0 g. of purified α -bromonaphthalene and 3.65 g. of magnesium, when the naphthylzinc chloride complex separated in part as lemon yellow crystals and in part as an oil which gradually solidified. After the addition of 200 cc. of benzene, the bulk of the ether was removed by distillation and a solution of 10.5 g. of Δ^4 -tetrahydrophthalic anhydride in 150 cc. of benzene was added dropwise with stirring to the boiling solution in the course of one hour; a gummy green precipitate separated. After refluxing for forty-five minutes longer, the reaction mixture was worked up in the usual way and the soda-extracted product obtained as an oil which soon solidified. Crystallization from aqueous methanol gave 11.1 g. (57%) of yellow prisms of the acid VII, m. p. 154–156.5°. A sample for analysis was crystallized twice from benzene-ligroin and three times from aqueous ethanol and obtained as clusters of light yellow prisms, m. p. 157–158.2°.

Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.37; H, 5.96.

In another experiment with 12.2 g. of anhydride the reaction was conducted under nitrogen and the first crop (7.5 g.) of the acidic product was obtained as colorless prisms, m. p. 123–146°. Two recrystallizations from aqueous alcohol afforded colorless, prismatic needles which melted partially at 143.6–145.8°, solidified, and remelted at 157.2–158.2°. A second crop of the material (6.4 g.) was yellowish and melted at 149–154°; total yield 62%. The best yield of VII realized in initial experiments utilizing α -naphthylmagnesium bromide was 41%.

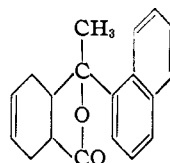
On one occasion α -naphthylzinc chloride was condensed with 30 g. of Δ^4 -tetrahydrophthalic anhydride in a nitrogen atmosphere under conditions much the same as described above except that the reaction mixture was refluxed for five hours. The total acidic fraction amounted to 22.5 g., m. p. 130–150°. This appeared to be a mixture, for seven crystallizations from benzene-ligroin and four crystallizations from aqueous alcohol gave in the top fraction a substance melting constantly at 171.6–173.2° and having the composition and properties of an isomeric 2-(α -naphthyl)-

Δ^4 -cyclohexene-1-carboxylic acid. When mixed with VII, this gave a depression of 20–25°.

Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.07; H, 5.42.

This stereoisomeric acid is not readily isomerized by alkali, for when 100 mg. of the substance was boiled with 4 cc. of 20% potassium hydroxide the recovered material melted initially at 160–167° and on recrystallization the main fraction melted at 169–171°.

α -(1'-Naphthyl)- α -methyl- Δ^4 -tetrahydrophthalide.—A



solution of 5 g. of 2-(α -naphthoyl)- Δ^4 -cyclohexene-1-carboxylic acid in 75 cc. of methanol was saturated with hydrogen chloride and refluxed for three hours and the ester was collected by ether extraction and distilled at 2 mm., b. p. 205–208°, as a viscous yellowish oil (4.6 g., 88%). To a stirred solution of 4 g. of the ester in 100 cc. each of benzene and ether there was added in one-half hour the Grignard solution (100 cc.) from 0.5 g. of magnesium and excess methyl bromide. After stirring and refluxing for two hours, the mixture was worked up; the soda-soluble fraction yielded no crystalline material, but the neutral fraction when manipulated with benzene-ligroin afforded 0.6 g. (16%) of prisms softening at 176° and melting at 185–187°. Three recrystallizations from benzene-hexane (colorless prisms) and two from aqueous alcohol (needles) gave material of the constant melting point 189–189.6° (soluble in boiling alkali).

Anal. Calcd. for $C_{19}H_{18}O_2$: C, 81.98; H, 6.52. Found: C, 81.72, 81.84; H, 6.85, 6.58.

2-(α -Naphthoyl)-cyclohexane-1-carboxylic Acid (VIII).—A solution of 5.6 g. of the unsaturated keto acid VII in 125 cc. of absolute ethanol in the presence of 100 mg. of Adams catalyst absorbed the theoretical amount of hydrogen at 25° in twenty minutes. Initial crystallization from aqueous alcohol gave 5 g. (89%) of colorless needles, m. p. 165–169°. After three recrystallizations the acid melted at 172.6–174°.

Anal. Calcd. for $C_{19}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.61; H, 6.15.

An isomeric 2-(α -naphthoyl)-cyclohexane-1-carboxylic acid was obtained by similar low-pressure hydrogenation of the high-melting unsaturated keto acid (15.1 g., m. p. 162–168°). The product crystallized from aqueous ethanol in small, colorless granules, m. p. 167–170° (13.4 g.) and on further purification formed prismatic needles, m. p. 169.2–171.1°; a mixture of this sample with the isomer VIII showed a depression of 18°.

Anal. Calcd. for $C_{19}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.46; H, 6.21.

When hydrogenated over copper chromite without solvent, this acid gave 2-(α -naphthylmethyl)-1-carboxylic acid, m. p. 199.5–200.9°, giving no depression with the sample described below.

2-(α -Tetrahydromethyl)-cyclohexane-1-carboxylic Acid (IX).—A slightly alkaline aqueous solution of 4.2 g. of 2-(α -naphthoyl)-cyclohexane-1-carboxylic acid (m. p. 174°) with 0.75 g. of copper-chromite catalyst (37KAF) was hydrogenated at an initial pressure of 2250 lb. at 150–190° for twenty-four hours. After acidification and extraction with ether, the product crystallized from benzene–ligroin as small, colorless prisms, m. p. 154–156°; yield 0.75 g. (18.5%). Two recrystallizations from aqueous alcohol afforded prismatic needles (0.47 g.), m. p. 160.2–161°.

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.53; H, 9.20.

1',2',3',4',5,6,7,8,9,10,10a,8a-Dodecahydro-1,2-benzanthrone-10 (X).—Treatment of 750 mg. of IX with liquid hydrogen fluoride (25 g.) for five minutes and crystallization of the product from acetone gave 250 mg. (36%) of colorless needles, m. p. 168–172°. The fully purified ketone formed glistening needles, m. p. 172.1–173.6°.

Anal. Calcd. for $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found: C, 85.18; H, 8.95.

For degradation, a solution of 1.1 g. of the ketone in 15 cc. of benzene was mixed with 20 g. of zinc dust in a 50-cc. distilling flask, the solvent was evaporated at the water pump, and sufficient zinc dust was added to fill the flask three-quarters full. The mixture was heated in a nitrite bath at dull red heat as long as any material distilled (forty-five minutes). Crystallization of the distillate from benzene–alcohol gave 300 mg. of yellow leaflets, m. p. 128–143°, and after further recrystallizations (three) the product formed yellowish plates, m. p. 155.5–156.2° and showed no depression when mixed with authentic 1,2-benzanthracene, m. p. 159.1–160.6°. Oxidation to the quinone gave material melting at 164–166°, and this likewise did not depress the m. p. of an authentic sample.

2-(α -Naphthylmethyl)-cyclohexane-1-carboxylic Acid (XI).—A mixture of 17.6 g. of 2-(α -naphthoyl)-cyclohexane-1-carboxylic acid and 2 g. of copper chromite catalyst (37KAF) in a glass liner²⁶ was shaken with hydrogen at an initial pressure of 1190 lb. at 170° for three hours, and the resulting greenish, glassy solid was extracted with boiling 10% soda solution. After clarification with Darco, the product obtained on acidification was crystallized from benzene–ligroin, giving 7.5 g. (44.7%) of small, colorless needles, m. p. 195.5–198.5°. Two further crystallizations afforded fine, glistening needles, m. p. 202–203°.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.80; H, 7.57.

The yield reported was duplicated in other hydrogenations conducted without solvent, and this proved to be the best of numerous methods tried. Reduction of the keto acid by Martin's toluene method²⁷ afforded the desired XI in 23.5% yield when the refluxing was continued for twenty-four hours. When the reaction was stopped after refluxing for only eleven hours, no reduced acid could be isolated. With a reflux period of seventy-two hours, XI was obtained in 10.5% yield and in addition there was isolated 7% of a neutral product having the composition of α -naphthylmethylcyclohexane. The purified substance

(26) Hershberg and Weiner, *Ind. Eng. Chem., Anal. Ed.*, **11**, 193 (1939).

(27) Martin, *THIS JOURNAL*, **58**, 1438 (1936).

crystallized from alcohol in fine, colorless, glistening needles, m. p. 124–125.3°; the trinitrobenzene derivative formed golden yellow needles from alcohol and melted at 131.2–132.6°.

Anal. Calcd. for $C_{17}H_{20}$: C, 91.01; H, 8.99. Found: C, 91.36; H, 9.28.

Clemmensen–Martin reduction of the methyl ester of the keto acid VIII gave only 9% of the reduced acid, m. p. 199.5–202.1°, and reduction of the acid or ester in acetic acid solution or in benzene–methanol or at a low temperature proved even less satisfactory. Experiments with zinc and alkali, sodium amalgam, and phosphorus and potassium iodide were unsuccessful.

5,6,7,8,9,10,10a-Octahydro-1,2-benz-10-anthrone (XII).—A solution of 8.2 g. of 2-(α -naphthylmethyl)-cyclohexane-1-carboxylic acid in 80 g. of hydrogen fluoride was allowed to stand at room temperature for three minutes and poured onto ice. The product, collected and washed in ether, crystallized from benzene–alcohol as colorless plates, m. p. 143–147°; yield 6.0 g. (78.5%). The analytical sample melted at 150–151.5°.

Anal. Calcd. for $C_{18}H_{18}O$: C, 86.36; H, 7.25. Found: C, 86.20; H, 7.36.

Dehydro-octahydro-1,2-benzanthryl-10-acetic Acid.—This acid was obtained in low yield as a product of the Reformatsky condensation of 600 mg. of the ketone XII with methyl bromoacetate under the usual conditions. A total of 280 mg. of the starting ketone was recovered unchanged by crystallization, and the oily residue on distillation and saponification with methyl alcohol–potassium hydroxide afforded 60 mg. of an acidic product, m. p. 181–190°. After further crystallizations from aqueous ethanol the acid formed colorless, silken needles, m. p. 193.4–195.5°, with previous sintering at 185°.

Anal. Calcd. for $C_{20}H_{20}O_2$: C, 82.16; H, 6.90. Found: C, 82.34; H, 7.23.

5,6,7,8,8a,9,10,10a-Octahydro-1,2-benz-10-anthranol.—A solution of 6 g. of the ketone XII and 15.9 g. of distilled aluminum isopropoxide in 50 cc. of dry toluene and 50 cc. of isopropyl alcohol (distilled over sodium) was refluxed and allowed to distil slowly for one hour; 100 cc. more toluene was added and slow distillation was continued for five hours, when a test for acetone with 2,4-dinitrophenylhydrazine was negative. The cooled mixture was taken up in ether and poured into 150 cc. of cold 10% hydrochloric acid. The product collected from the washed organic layer when crystallized from aqueous ethanol gave 5.0 g. (82%) of silken needles melting at 137–152° and suitable for the next step. The fully purified carbinol melted at 169.2–170.2°.

*Anal.*²⁵ Calcd. for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.49; H, 8.37.

10-Chloro-5,6,7,8,8a,9,10,10a-octahydro-1,2-benzanthracene (XIII).—Dry hydrogen chloride was passed into a suspension of 6.7 g. of the above carbinol in 150 cc. of cold benzene; within fifteen minutes the solid dissolved to give a turbid solution. After continued introduction of gas for fifteen minutes, the solution was dried over calcium chloride and evaporated to dryness in vacuum at room temperature. Crystallization of the residue from ether–petroleum ether gave 5.5 g. (76%) of colorless prismatic

needles, m. p. 109–113°, dec. Recrystallization of a sample from ether–petroleum ether gave both prismatic plates, m. p. 106.5–112°, dec., and needles, m. p. 119.6–121.6°, dec.; a mixture of the two forms melted at 109–113°.

*Anal.*²⁵ Calcd. for $C_{18}H_{19}Cl$: C, 79.83; H, 7.07. Found: C, 79.96; H, 7.41.

5,6,7,8,8a,9,10,10a-Octahydro-1,2-benzanthracene-10-acetic Acid (XV).—A solution prepared under nitrogen from 1.38 g. of sodium and 30 cc. of absolute ethanol was treated with stirring with 9.6 g. of diethylmalonate. Excess ethanol was distilled in a current of nitrogen and a solution of the residue in 50 cc. of dry benzene was cooled in ice and treated with 5.44 g. of the 10-chlorooctahydrobenzanthracene in 20 cc. of benzene. The mixture was allowed to warm to room temperature with stirring in the course of four hours, then heated for fourteen hours over a 40-watt light bulb, and finally refluxed on a steam-bath for three hours. The benzene was evaporated in a current of air and the residue refluxed for two hours with 50 cc. of 35% potassium hydroxide. After cooling, neutral material was removed by ether extraction and the alkaline solution was acidified. The oily acidic fraction was collected by ether extraction and heated in an oil-bath at 180–190° for ten minutes, to effect decarboxylation. The resulting viscous oil was clarified with Darco in benzene solution, and the concentrated filtrate after dilution with ligroin deposited 1.65 g. (28%) of the acidic product in the form of small, pale tan needles, m. p. 169–178°. A sample after three recrystallizations melted at 180.5–182°.

*Anal.*²⁵ Calcd. for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.83; H, 7.29.

5,6,7,8,8a,9-Hexahydro-1,2-benzanthracene (XIV).—The material recovered from the ethereal extract of the neutral fraction resulting from the above saponification was taken up in benzene and passed through a tower of activated alumina; the filtrate when concentrated and diluted with ligroin yielded 1.0 g. of colorless crystals, m. p. 98–110°. Further purification from benzene–ligroin gave colorless, rhombic prisms (0.5 g.), m. p. 117.8–118.8°.

*Anal.*²⁵ Calcd. for $C_{18}H_{18}$: C, 92.26; H, 7.74. Found: C, 92.35; H, 8.15.

5,6,7,8,8a,9,10,10a-Octahydro-1,2-benzanthracene was obtained by hydrogenation of the hexahydride in absolute ethanol in the presence of Adams catalyst. Crystallization from ethanol–benzene gave glistening needles, m. p. 125.8–126.4°.

Anal. Calcd. for $C_{18}H_{20}$: C, 91.47; H, 8.53. Found: C, 91.42; H, 8.20.

4a'-Keto-5,6,7,8,8a,9,10,10a-octahydro-1,2-benzanthracene (XVI).—Cyclization of the acetic acid derivative (XV) (2.0 g.) with hydrogen fluoride (20 g.) was conducted at room temperature, and after three minutes the solution was poured onto ice. The precipitated solid was washed with soda in ether–benzene solution, and the solution when dried and concentrated yielded 1.07 g. of pale tan needles, m. p. 198–201°, and 0.08 g., m. p. 171–188°; total yield 61%. A sample after two recrystallizations from benzene–ligroin formed pale lemon-yellow needles, m. p. 200.4–201.4°.

*Anal.*²⁵ Calcd. for $C_{20}H_{20}O$: C, 86.91; H, 7.30. Found: C, 86.98; H, 7.09.

Acidification of the soda washings gave 0.27 g. of an acidic substance, m. p. 208–211°, which appears to be an isomer of XVI. On crystallization from benzene–ligroin the acid formed small, pale tan needles, m. p. 210.5–212°.

*Anal.*²⁵ Calcd. for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 82.10; H, 7.35.

When cyclized with hydrogen fluoride this acid (0.21 g.) yielded a ketone isomeric with XVI (70 mg., m. p. 146–154°). The substance crystallized from benzene–ligroin in heavy yellow needles, m. p. 154–158° (50 mg.).

*Anal.*²⁵ Calcd. for $C_{20}H_{20}O$: C, 86.91; H, 7.30. Found: C, 86.93; H, 7.01.

4a'-Hydroxy-5,6,7,8,8a,9,10,10a-octahydro-1,2-benzanthracene (XVII).—A solution of 1.0 g. of the ketone XVI (m. p. 198–201°) and 5 g. of aluminum isopropoxide in 25 cc. of benzene and 50 cc. of isopropyl alcohol was distilled slowly through a 23-cm. column for one and one-quarter hours, 50 cc. of toluene was added and slow distillation continued for three and one-half hours. The resulting carbinol separated as a solid on decomposition with dilute hydrochloric acid and was brought into solution in ether–benzene by the addition of alcohol. Evaporation to dryness in vacuum left a crystalline residue of 0.98 g. (97%) of colorless material, m. p. 208–210°. Recrystallization from acetone formed a substance of lustrous fine needles, m. p. 211–213°.

*Anal.*²⁵ Calcd. for $C_{20}H_{22}O$: C, 86.29; H, 7.97. Found: C, 86.23; H, 7.67.

4,10-Ace-1,2-benzanthracene (XVIII).—A solution of 270 mg. of the carbinol XVII in 8 cc. of α -methyl-naphthalene (distilled over sodium) was refluxed with 250 mg. of palladium charcoal in an all-glass boiler swept with carbon dioxide¹⁴ for three and one-quarter hours; 200 mg. more catalyst was then added and refluxing continued for seven hours longer, when the evolution of hydrogen ceased. The mixture was extracted with ether and the α -methyl-naphthalene was removed by distillation at 1 mm. (b. p. 75°); the solidified residue then crystallized from ether in small orange needles, m. p. 120–131°. This material was combined with 70 mg. of similar product from a previous run and recrystallized from ether; the first crop consisted mainly of the sparingly soluble and easily separated 4a'-keto-4,10-ace-1,2-benzanthracene, m. p. 188–205° (30 mg., see below). Concentration of the mother liquor afforded 200 mg. of orange needles of the hydrocarbon, m. p. 129–139°, which on recrystallization melted at 140–144°. After further purification the substance formed glistening, pale tan needles, m. p. 144.6–146°. A mixture of the substance with a sample of the hydrocarbon synthesized by Fieser and Seligman¹⁹ (m. p. 135–139°) showed no depression.

*Anal.*²⁵ Calcd. for $C_{20}H_{14}$: C, 94.45; H, 5.55. Found: C, 94.77; H, 5.61.

The picrate formed deep reddish brown needles from benzene and melted at 154.6–156° (F. and S.,¹⁹ 148–149°).

*Anal.*²⁵ Calcd. for $C_{20}H_{14}C_6H_5O_7N_3$: C, 64.60; H, 3.54. Found: C, 64.73; H, 3.39.

4a'-Keto-4,10-ace-1,2-benzanthracene (XIX).—The high-melting material which separated from the dehydrogenation mixture crystallized from ether in glistening,

bright yellow needles melting largely at 230–232° but giving a clear melt at 233.3°.

*Anal.*²⁵ Calcd. for C₂₀H₁₂O: C, 89.53; H, 4.51. Found: C, 89.65; H, 4.75.

Summary

Δ⁴-Tetrahydrophthalic anhydride reacts with arylmagnesium or arylzinc halides to give unsaturated keto acids in reasonably good yield, and the hexahydride when condensed with benzene in the presence of aluminum chloride affords 2-benzoylcyclohexane-1-carboxylic acid in excellent yield. The use of hydro derivatives of phthalic anhydride in syntheses in the anthracene and 1,2-benzanthracene series expands the possibilities

for synthetic operations, particularly since the hydro derivatives of the intermediate anthrones are stable in the ketonic form and hence amenable to additions, or to reduction to the carbinols. Thus a new synthesis of 4,10-ace-1,2-benzanthracene has been worked out starting with the condensation of α-naphthylzinc chloride and Δ⁴-tetrahydrophthalic anhydride. The hydrocarbon obtained has a higher melting point than products prepared by two earlier syntheses and shown to possess considerable carcinogenic potency.

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Sterols. CXXXVI. Sapogenins. LVII. The Structure of the Side-Chain of Chlorogenin

BY RUSSELL E. MARKER, D. L. TURNER AND EMERSON L. WITTBECKER

Diosgenin was shown recently to have the carbon skeleton of cholesterol by converting it to a mixture of cholesterol and 5-cholestene.¹ The method employed to effect this conversion has now been extended to chlorogenone (II). The reduction of chlorogenone by the Clemmensen method followed by halogenation and reduction gave cholestane (VII). This provides additional proof that chlorogenin is similar to the other sapogenins in its carbon skeleton and that it has the same steric configuration as cholestane. Conditions have been found by Marker and Rohrmann² which enable the nuclear carbonyl groups of chlorogenone to be removed by reduction with zinc and hydrochloric acid without alteration of the side-chain. The resulting desoxychlorogenin (III) was identical with desoxytigogenin. That the side-chain in this substance is intact has been shown by the conversion of desoxychlorogenin (III) to 16-*allo*-pregnen-20-one (IX) using the method of Marker and Rohrmann.³ This involves the oxidation of pseudo-desoxychlorogenin (VI) with chromic anhydride and hydrolysis of the oxidation product. The 16-*allo*-pregnen-20-one (IX) was reduced to *allo*-pregnan-20-one (XIII) which was identified by comparison with a sample obtained from *allo*-pregnan-3,20-dione.⁴

A substance obtained by the catalytic reduction of chlorogenone in neutral medium and designated β-chlorogenin (V) was assumed to differ from chlorogenin only in the configuration of the C-6 hydroxyl group.⁵ That this is indeed the case has now been shown by the preparation of pseudo-β-chlorogenin (VIII) and by the oxidation of its acetate to a substance which on hydrolysis gives 16-*allo*-pregnen-3,6-diol-20-one (XI). When pseudo-β-chlorogenin was oxidized without prior acetylation and the product was hydrolyzed, 16-*allo*-pregnen-3,6,20-trione (X) was obtained. This is identical with the substance previously described.⁶ The other hydrolysis product, α-methylglutaric acid (XII), was also isolated.⁷ This indicates that the side-chain of pseudo-β-chlorogenin is identical with that assigned to the other pseudosapogenins.^{7,8}

The catalytic reduction of 16-*allo*-pregnen-3,6-diol-20-one (XI) and of 16-*allo*-pregnen-3,6,20-trione (X) led to the same product in each case, *allo*-pregnan-3(β),6(β),20(β)-triol (XIV). The behavior of 16-*allo*-pregnen-3,6,20-trione on reduction is thus similar to that of chlorogenone.⁵

We wish to thank Parke, Davis and Company for their generous help.

(1) Marker and Turner, *THIS JOURNAL*, **63**, 767 (1941).
(2) Marker and Rohrmann, *ibid.*, **61**, 946 (1939).
(3) Marker and Rohrmann, *ibid.*, **62**, 518 (1940).
(4) Marker and Lawson, *ibid.*, **61**, 852 (1939).

(5) Marker, Jones and Turner, *ibid.*, **62**, 2537 (1940).
(6) Marker, Jones, Turner and Rohrmann, *ibid.*, **62**, 3006 (1940).
(7) Cf. Marker, *et al.*, *ibid.*, **63**, 779 (1941).
(8) Marker, *et al.*, *ibid.*, **63**, 774 (1941).