Anal. Calcd. for $C_{18}H_{18}O_2Br_2$: C, 50.69; H, 4.26. Found: C, 50.87; H, 4.38.

The **diacetate** was prepared by refluxing 0.3 g. of the high-melting enediol in 20 cc. of acetic anhydride for three hours. The product was recrystallized from high-boiling petroleum ether; m. p. 241–242°; yield 0.3 g.

Anal. Calcd. for $C_{22}H_{22}O_4Br_2$: C, 51.74; H, 4.35. Found: C, 51.47; H, 4.42.

A **dibenzoate** of the enediol was prepared by refluxing a mixture of 0.3 g. of the enediol, 5 cc. of benzoyl chloride and 20 cc. of pyridine for three hours. The dibenzoate crystallized from a mixture of benzene and absolute alcohol in glistening white leaflets; m. p. 265–267°; yield 0.28 g.

Anal. Calcd. for $C_{32}H_{26}O_4Br_2$: C, 60.55; H, 4.13. Found: C, 60.76; H, 4.27.

Reaction of 4,4′-Dibromo-2,6-xylil with Hydroxylamine.—A mixture of 0.5 g. of hydroxylamine hydrochloride, 0.5 g. of potassium hydroxide, 0.3 g. of the diketone and 20 cc. of ethanol was heated under reflux overnight. The light orange solution was cooled, poured into 200 cc. of water and the mixture made slightly acidic with dilute hydrochloric acid. The white, flocculent precipitate which formed was extracted with ether; the ether solution was washed with water, 10% potassium bicarbonate solution, and again with water. It was then treated with Norit, filtered and the ether was evaporated. The residue separated from a benzene–high-boiling petroleum ether mixture in fine, white crystals; m. p. 222–223°; yield 0.28 g.

Anal. Calcd. for $C_{18}H_{17}O_2NBr_2$: C, 49.19; H, 3.90; N, 3.19. Found: C, 49.41; H, 3.97; N, 3.18.

The melting points and analytical data for the new compounds in the mesityl and triethylphenyl series have been collected in Table I.

Summary

Enediols have been prepared from 4,4′-dibromo-2,6-xylil (II), from 3,3′-dibromomesitil (IV, R = CH_3) and from 3,3′-dibromohexaethylbenzil (IV, R = C_2H_5). Those in which the bromine atoms are meta to the diol group are not greatly different from the corresponding bromine-free compounds. Bromine atoms which are in positions para to the diol group, however, render the enediols much more sensitive to oxidation by the air.

URBANA, ILLINOIS RECEIVED MARCH 31, 1941

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

Some Modifications of the Synthesis of 3,4-Benzpyrene from Pyrene

BY W. E. BACHMANN, MARVIN CARMACK[1] AND S. R. SAFIR

In the Cook and Hewett[2] synthesis of the carcinogenic hydrocarbon 3,4-benzpyrene, pyrene is condensed with succinic anhydride, the resulting β-3-pyrenoylpropionic acid (I) is reduced to γ-3-pyrenylbutyric acid, the latter is cyclized to 4′-ketotetrahydrobenzpyrene and the ketone is converted to the hydrocarbon. In this paper we are reporting some modifications of this synthesis which we found useful for preparing the hydrocarbon.[3]

Usually β-aroylpropionic acids are reduced by the Clemmensen method, but Cook and Hewett[2] and also Martin[4] have shown that the method fails with β-3-pyrenoylpropionic acid. Neither the acid nor its ester was reduced by zinc and hydrochloric acid with or without the use of toluene, and the employment of acetic acid in the reducing mixture resulted in the formation of resinous products. Although Cook and Hewett succeeded in reducing the keto acid by means of zinc and alkali, a reaction which Vollmann, Becker, Corell and Streeck[5] carried out most successfully in an autoclave at 80–100 atmospheres pressure, it seemed desirable to reinvestigate the Clemmensen method because of the simplicity of the procedure employed and because it was of interest to know whether conditions could be found for reducing the compound by this method. After considerable experimentation, it was found that the keto acid is reduced to γ-3-pyrenylbutyric acid when a mixture of chlorobenzene, xylene and acetic acid is used in the Clemmensen mixture. The yields of fairly pure reduced acid varied from 68 to 84% and depended chiefly on the amounts being reduced. It is noteworthy that under the conditions employed the reaction proceeds extremely rapidly for a Clemmensen reaction in spite of the slight solubility of the keto acid; thus, on a 2-g. run a 70% yield of the reduced acid was obtained when only two hours were allowed for the reaction.

A small amount of a rather insoluble colorless solid is formed as a by-product in the reaction;

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(1) From the Ph.D. dissertation of Marvin Carmack.

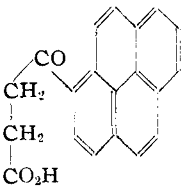
(2) Cook and Hewett, *J. Chem. Soc.*, 398 (1933).

(3) Fieser [*Am. J. Cancer*, **34**, 76 (1938)] has discussed the relative merits of the procedures that have been employed to prepare the hydrocarbon and its intermediates.

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

(5) Vollmann, Becker, Corell and Streeck, *Ann.*, **531**, 1 (1937).

when no acetic acid was employed in the reducing mixture as much as 35% of the compound was formed in small runs. Although the structure of the compound has not been established definitely, we consider the compound to be one of the two possible dilactones of the pinacol. This structure is indicated by the insolubility of the compound in cold aqueous alkali and its cleavage by hot concentrated alcoholic potassium hydroxide to the salts of the keto acid (I) and the corresponding hydroxy acid, γ-3-pyrenyl-γ-hydroxybutyric acid.



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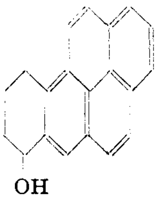

II

Another modification of the synthesis was introduced in the conversion of 4′-ketotetrahydrobenzpyrene to 3,4-benzpyrene. This has been accomplished by other investigators by heating the cyclic ketone with selenium preferably after preliminary reduction with sodium and alcohol[2]; by high-pressure catalytic reduction of the ketone to tetrahydrobenzpyrene followed by selenium dehydrogenation of the latter at 330° for thirty-six hours[6]; and by zinc dust distillation of the ketone. The latter method, suggested by Fieser and Fieser[6] for small amounts, was employed on a fairly large scale by Vollmann and co-workers[5] who considered this method to be the best one available. We have found that the conversion can be accomplished readily by first reducing the cyclic ketone to the corresponding secondary alcohol (II) by means of aluminum isopropoxide and then dehydrating and dehydrogenating the alcohol to 3,4-benzpyrene by means of palladium on charcoal. In a run in which all of the crude secondary alcohol was used in the second step without purification, the over-all conversion of the ketone to the hydrocarbon was 80%.

Experimental

β-3-Pyrenoylpropionic acid (I) was prepared by the method of Cook and Hewett[2] except that the Friedel-Crafts reaction was started at −5° and the mixture was stirred at −5 to 0° for only three hours after the addition of the pyrene (instead of keeping it at room temperature for twenty-four hours); then it was hydrolyzed and steam distilled. The sodium salt of the keto acid was precipitated from its solution by means of sodium chloride,[6] filtered, and washed with acetone. The free acid obtained from the sodium salt was purified further by boiling a solution of its ammonium salt with Norit and reprecipitating the acid. The yield of light yellow acid melting at 180–182° from 50 g. of pyrene was 64–68 g. Recrystallization from six volumes of a 3:1 mixture of xylene and acetic acid gave 61.5–63.5 g. (82–87%) of the acid; m. p. 181.5–182.5°. Vollmann and co-workers,[5] using the Cook and Hewett procedure, obtained an 82% yield of recrystallized acid (m. p. 184°) and Fieser and Fieser[6] reported a 90–94% yield of the sodium salt of the acid by their method in which sixteen hours were allowed for the reaction.

The **methyl ester** was formed when 5 g. of the keto acid was refluxed for one hour with 50 cc. of methanol saturated with hydrogen chloride. On cooling, a 95% yield of the ester separated as yellow rhombic crystals; m. p. 106–106.5°. Further purification by evaporative distillation at 0.01 mm. and recrystallization from methanol raised the melting point to 108–108.5°.

Anal. Calcd. for $C_{21}H_{16}O_3$: C, 79.7; H, 5.1. Found: C, 79.2; H, 4.8.

Reduction of the Keto Acid.—After numerous trials in which the solvents, the relative proportions of the reagents and the time of heating were varied, the following procedure was adopted. Fifty g. of zinc (20-mesh) was cleaned by heating it with a solution of 5 cc. of 45% aqueous potassium hydroxide and 10 cc. of alcohol on a steam-bath for ten minutes; it was washed with water and with hydrochloric acid and then amalgamated with a solution of 2 g. of mercuric chloride in 40 cc. of water in acid solution. The amalgamated zinc, 30 cc. of concentrated hydrochloric acid, 30 cc. of acetic acid, 22.5 cc. of xylene and 7.5 cc. of chlorobenzene were placed in a 500-cc. round-bottomed flask in this order; 5 g. of recrystallized β-3-pyrenoylpropionic acid was then added carefully to the upper layer so that none of the solid dropped down on the zinc. After one-half hour of refluxing on a sand-bath the rather insoluble solid acid had disappeared. The mixture was refluxed for six hours; during this time two 10-cc. portions of concentrated hydrochloric acid were added. Usually some insoluble flocculent material (dilactone of the pinacol) appeared in the light transparent orange-red solution. The liquids were decanted from the zinc into a beaker (or alternately the mixture was allowed to cool in the flask until crystallization was complete when the crystals plus the zinc were filtered from the liquids); after about six hours of cooling the crystals of the product which had separated from the upper layer were filtered off, washed with water and a small amount of benzene and dried. The product (alone or with the zinc) was digested with a warm solution of 3 g. of sodium hydroxide in 150 cc. of water in order to separate the reduced acid from the insoluble colorless by-product (0.15–0.2 g.; m. p. 250–260°).

Acidification of the filtered alkaline solution yielded 3.7–3.78 g. of γ-3-pyrenylbutyric acid as a chalk white solid suitable for cyclization; m. p. 183.5–184.5°; with concentrated sulfuric acid it gave no trace of the red color given by the keto acid. From the xylene–chlorobenzene filtrate an additional 0.2–0.4 g. of satisfactory product was isolated (by warming the washed solution with dilute sodium hydroxide and recrystallizing the acid obtained from the alkaline solu-

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(6) Fieser and Fieser, THIS JOURNAL, **57**, 782 (1935).

tion from acetone and benzene) which brought the yield to 80–84%. When the acid (15 g.) was purified by dissolving it in hot acetone, boiling the solution with Norit, filtering, evaporating and recrystallizing the residue from a 3:1 mixture of xylene and acetic acid, slightly colored platelets (12.7 g.) of the acid were obtained; m. p. 186–186.5°.

On runs in which 25 g. of the keto acid was reduced (six hours being allowed for the complete reaction) an average yield of 16.2 g. (68%) of product (m. p. 183–184°) was obtained from the crystals which precipitated from the organic layer in the reaction mixture. In one 25-g. run, only 2.5 g. of the keto acid was added to the mixture (250 g. of zinc and proportionate amounts of the other reagents) at the start; after twenty minutes of refluxing, a 2.5-g. portion of the keto acid was added through the top of the condenser followed immediately by 10 cc. of concentrated hydrochloric acid, which washed down most of the acid clinging to the sides of the condenser tube. This operation was repeated every twenty minutes until all of the keto acid had been added; the mixture was then refluxed for three hours longer. The yield of acid (m. p. 183–184°) including that isolated from the xylene–chlorobenzene filtrate was 18.2 g. (76%).

Chlorobenzene without the addition of xylene was used satisfactorily in some runs, but occasionally the layer settled down on the zinc and the yield and purity of the product was poor. The xylene served to keep the organic layer on top of the aqueous solution. A large excess of zinc appeared to be essential for satisfactory results, for the success of the reaction depended on reducing a given amount of keto acid as rapidly as possible. The recovered zinc may be used in another reduction after being cleansed with nitric acid.

A number of runs were made on the methyl ester of the keto acid using toluene as the upper solvent layer. In one run a mixture of 3 g. of the ester, 10 cc. of toluene, 20 cc. of concentrated hydrochloric acid, 20 cc. of acetic acid and 20 g. of amalgamated zinc was refluxed for thirty-eight hours; during this time four 5-cc. portions of hydrochloric acid were added. When the mixture was cooled, 2 g. (69%) of γ-3-pyrenylbutyric acid crystallized from the toluene layer.

The **insoluble by-product** (1 g.) from several runs was heated with a solution of 2 g. of potassium hydroxide in 5 cc. of absolute ethanol on a steam-bath. After one-half hour the clear solution was evaporated, the residue was dissolved in water and the solution was acidified. The product which consisted of a mixture of the keto acid and the corresponding hydroxy acid was heated in xylene for one hour in order to convert the hydroxy acid to its lactone. Digestion of the product obtained from the xylene with water, methanol and ammonium hydroxide dissolved the keto acid and left the lactone (0.29 g.). The γ-3-pyrenyl-γ-butyrolactone after evaporative distillation at 0.01 mm. and two recrystallizations from acetic acid melted at 176–176.5° alone and when mixed with a sample prepared as described by Cook and Hewett.[2]

4′-Hydroxy-1′,2′,3′,4′-tetrahydro-3,4-benzpyrene (II).—The cyclic ketone 4′-ketotetrahydrobenzpyrene was prepared according to the excellent procedure of Fieser and Novello[7] except that the reaction of the γ-3-pyrenylbutyric acid (15 g., recrystallized) with phosphorus pentachloride and the cyclization of the acid chloride with stannic chloride were both carried out entirely at room temperature; one-half hour was allowed for the first step and eight hours for the second operation. In this manner 13.6 g. (96%) of light-yellow ketone, m. p. 168–171°, was obtained (reported,[7] 85–95%; m. p. 163–165°). After recrystallization from benzene the m. p. was 170–173°; yield, 90%. From 12.5 g. of unrecrystallized γ-3-pyrenylbutyric acid (as obtained by acidification of a solution of its sodium salt), 9.15 g. of the ketone, m. p. 169–170.5° (171–172° on remelting) and 0.52 g. melting at 168–169.5° were obtained; total yield, 83%. This material was suitable for the next step.

Clemmensen reduction of a sample of the ketone using toluene yielded **1′,2′,3′,4′-tetrahydro-3,4-benzpyrene** in 60% yield. After recrystallization from acetic acid, evaporative distillation at 0.01 mm. and recrystallization from ethanol large colorless plates of the hydrocarbon were obtained which melted at 113–113.5°, in agreement with Fieser and co-workers[6,8] and not with Winterstein, Vetter and Schön,[9] who reported a value of 135°.

Reduction of 5 g. of the cyclic ketone by a solution (not clarified) of aluminum isopropoxide prepared from 2.5 g. of polished aluminum wire and 50 cc. of anhydrous isopropyl alcohol (one-half hour of refluxing followed by slow distillation through an upright air condenser of 21 cc. of distillate in the course of one and one-half hours) gave 78–90% yields of satisfactory secondary alcohol (II) in four runs but in others the yield and purity of the product were less satisfactory. Good results were obtained consistently with a stock solution of *M* vacuum-distilled aluminum isopropoxide in isopropyl alcohol (warmed just before use in order to dissolve all of the reagent). A mixture of 5 g. of the ketone and 100 cc. of the stock solution was refluxed for one-half hour and then distilled for one and one-half hours so that 45 cc. of distillate was collected; 45 cc. of anhydrous isopropyl alcohol was added and distillation was continued for thirty minutes when no test for acetone was obtained in the distillate.[10]

The solution was poured into 300 cc. of ice-cold 5% hydrochloric acid and the nearly colorless secondary alcohol was filtered and washed well with water and then with ammonium hydroxide. A benzene solution of the product was washed well with ammonium hydroxide and then with water and the solvent was removed at 25° under reduced pressure. The residue was dissolved in hot acetone, the solution was boiled with Norit and filtered, and absolute alcohol was added to the concentrated solution. The first crop of practically colorless needles (m. p. 140–141.5°) weighed 3.45 g. and the second crop (m. p. 139–141°) weighed 0.51 g.; total yield, 79%). A sample after recrystallization from benzene melted at 141.5–142°. It was somewhat difficult to obtain it entirely free from solvent. The alcohol gives an intense purple color with concentrated sulfuric acid.

Anal. Calcd. for $C_{20}H_{16}O$: C, 88.2; H, 5.9. Found: C, 88.9; H, 6.2.

3,4-Benzpyrene.—Two grams of the cyclic ketone (prepared from unrecrystallized γ-3-pyrenylbutyric acid) was

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[7] Fieser and Novello, This Journal, **62**, 1855 (1940).

[8] Fieser and Hershberg, *ibid.*, **60**, 1658 (1938).

[9] Winterstein, Vetter and Schön, *Ber.*, **68**, 1079 (1935).

[10] Lund, *ibid.*, **70**, 1520 (1937).

reduced in the manner described and the crude alcohol (obtained by pouring the mixture into dilute hydrochloric acid, filtering and washing the solid with water and with ammonium hydroxide) without purification was heated with 0.2 g. of palladium–charcoal catalyst[11] in a large test-tube in an atmosphere of nitrogen at 310–320° for one and one-half hours. The material which had sublimed up along the sides of the tube was washed down with benzene, the solvent was evaporated and heating was continued for an additional two hours.

The product was separated from the catalyst by means of hot benzene, the solution was passed through a tower of alumina, the solvent was removed under reduced pressure and the 3,4-benzpyrene was recrystallized from benzene–methanol. The first two crops (1.55 g.) were combined and evaporatively distilled at 200–210° at 0.01 mm.; this left behind a trace of high-melting impurity. The product was dissolved in hot acetone, an equal volume of *n*-propyl alcohol was added and the solution was concentrated to incipient crystallization. On cooling, the 3,4-benzpyrene crystallized in large, thin sheets, which began to change to long, pale-yellow needles after a short time; the complete change required an hour or two. The first crop (1.43 g.) melted at 177.5–178.5° cor. (vac.) with slight previous softening and remelted at 178–179°; the second crop (0.05 g.) melted at 175–176° cor.; total yield, 80%. A slightly higher yield of the hydrocarbon was obtained when recrystallized secondary alcohol was used.

A sample was purified further by making and recrystallizing the picrate, and passing the regenerated hydrocarbon through alumina; after recrystallization it melted at 178.6–179.8° cor. (vac.) with slight previous softening and remelted at 179–180° cor. (highest previously recorded value, 178.8–179.3° cor.[12]).

Summary

A procedure has been devised for reducing β-3-pyrenoylpropionic acid to γ-3-pyrenylbutyric acid by the Clemmensen method.

A new procedure for obtaining the carcinogenic hydrocarbon 3,4-benzpyrene from 4′-ketotetrahydrobenzpyrene in good yield is described. The cyclic ketone is reduced to the corresponding alcohol by means of aluminum isopropoxide and the alcohol is dehydrated and dehydrogenated to the hydrocarbon by palladium on charcoal.

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[11] Zelinsky and Turowa-Pollak, *Ber.*, **58**, 1295 (1925).

[12] Fieser and Newman, THIS JOURNAL, **57**, 1602 (1935).

ANN ARBOR, MICHIGAN RECEIVED JANUARY 15, 1941

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

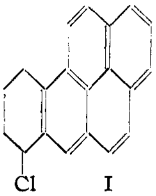
4′,5-Dimethylene-3,4-benzpyrene

BY W. E. BACHMANN AND MARVIN CARMACK[1]

The polycyclic hydrocarbon 4′,5-dimethylene-3,4-benzpyrene (VI) is of particular interest in that it combines in one molecule the structural features of the two powerful carcinogens 3,4-benzpyrene and cholanthrene. We were interested in determining whether this compound would surpass its two prototypes in carcinogenic activity.

For its synthesis 4′-chlorotetrahydrobenzpyrene (I) was converted to 4′-tetrahydrobenzpyrenylacetic acid (III) through the malonic ester synthesis, and the acid was cyclized in practically quantitative yield to the ketone IV. A by-product in the malonic ester reaction was 1′,2′-dihydro-3,4-benzpyrene (II), which was formed by elimination of the elements of hydrogen chloride from the chloride I. This hydrocarbon was prepared also by heating the chloride with pyridine. As was expected, the dihydro derivative was easily dehydrogenated by palladium to 3,4-benzpyrene.

After a number of unsuccessful trials to reduce the cyclic ketone (IV) by the Clemmensen method and by the Wolff–Kishner reaction, the following method was evolved for obtaining the desired hydrocarbon. The ketone was reduced by means of aluminum isopropoxide and the resulting alcohol was dehydrated to a yellow hydrocarbon to which the structure V is assigned. When this hydrocarbon was heated with palladium on charcoal, it lost hydrogen and was converted to the beautifully crystalline orange colored 4′,5-dimethylene-3,4-benzpyrene (VI).



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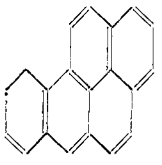

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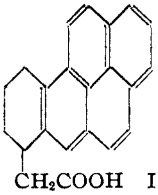

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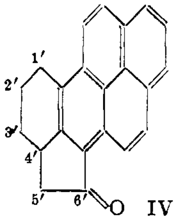

IV

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[1] From the Ph.D. dissertation of Marvin Carmack.