JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

VOLUME 63 FEBRUARY 6, 1941 NUMBER 2

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Synthesis of 10-Methyl-3′-isopropyl-1,2-benzanthracene from 9,10-Dihydroretene

BY LOUIS F. FIESER AND RICHARD C. CLAPP

The 9,10-dihydro derivatives of phenanthrene[1,2] and of 4,5-methylenephenanthrene[3] have been found to undergo smooth succinoylation with exclusive substitution at the 2-position para to the diphenyl linkage, and cyclization of the γ-arylbutyric acids resulting on reduction of the keto acids affords in good yields ketones of the 1,2-benzanthracene series. From analogy with these cases, 9,10-dihydroretene (II) would be expected to yield the 2-succinoyl derivative, III, and provide a route to 10-methyl-3′-isopropyl-1,2-benzanthracene, or 2,3-benzoretene (VII). Adelson and Bogert[4] investigated the succinoylation of retene itself and obtained in 58.5% yield a keto acid which they regarded as the 6-isomer on the basis of a correlation[5] with the B-retenol studied by Fieser and Young.[6] The acid was utilized in the synthesis of a hydrocarbon designated "5,6-benzoretene." The observations from this Laboratory[6] had indicated that the B-retenol probably is either the 3- or the 6-isomer, and on the basis of minor considerations which are now recognized as invalid we expressed a preference for the latter formulation. Recently Campbell and Todd[7] reexamined the question and succeeded in proving that the compounds of the B-series are 3-derivatives. The hydrocarbon of Adelson and Bogert, they note, therefore is either 2,3- or 3,4-benzoretene. A synthesis of the former isomer, which is of interest for its possible carcinogenicity, would settle this structural problem.

9,10-Dihydroretene, obtained by Nyman[8] in 60% yield by reduction of the hydrocarbon with sodium and amyl alcohol, was prepared conveniently by high-pressure hydrogenation over copper chromite catalyst at 160°. In contrast to the behavior noted with phenanthrene,[2] there was little tendency for the reduction to proceed beyond the dihydro stage. On succinoylation of 9,10-dihydroretene in nitrobenzene solution only one acidic product was encountered and this was obtained in 80% yield. Although substitution is perhaps not quite as uniform as with the other two 9,10-dihydrides mentioned above (96–99% yields), it is considerably more so than in the case of retene, from which we obtained the keto acid of Adelson and Bogert in even lower yield than reported. Reduction of the dihydro keto acid was accomplished most satisfactorily by high-pressure hydrogenation of the sodium salt in aqueous solution, and the γ-retylbutyric acid was cyclized in excellent yield with liquid hydrogen fluoride. High-pressure hydrogenation of the ketone gave a crystalline low melting (46°) hexahydride which underwent very smooth dehydrogenation when heated with palladium charcoal and afforded pure benzoretene in very good yield.

The ultraviolet absorption spectrum of the hydrocarbon was determined by Dr. R. N.

---

[1] Burger and Mosettig, THIS JOURNAL, **59**, 1305 (1937).

[2] Fieser and Johnson, *ibid.*, **61**, 168 (1939).

[3] Fieser and Cason, *ibid.*, **62**, 1293 (1940).

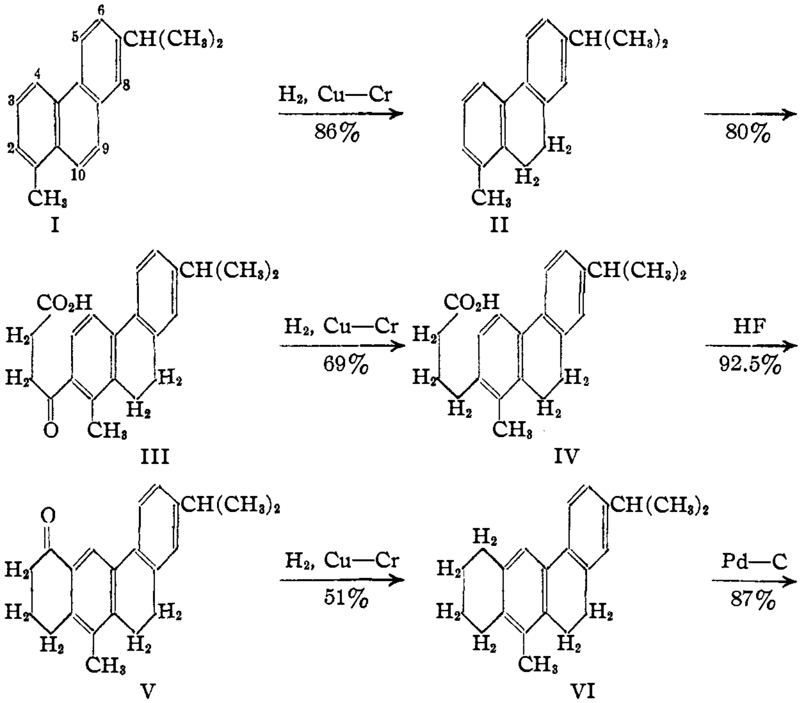
[4] Adelson and Bogert, *ibid.*, **59**, 399, 1776 (1937).

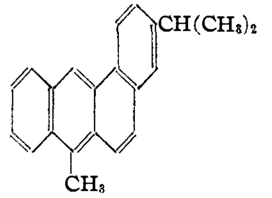
[5] Adelson and Bogert, *ibid.*, **58**, 653 (1936).

[6] Fieser and Young, *ibid.*, **53**, 4120 (1931).

[7] Campbell and Todd, *ibid.*, **62**, 1287 (1940).

[8] Nyman, *Ann. Acad. Sci. Fennicae*, **A41**, No. 5 (1934); *Chem. Abst.*, **30**, 2958 (1936).





VII

Jones[9] and found to correspond in every respect to the pattern characteristic of the alkyl 1,2-benzanthracene derivatives. The only possible benzoretene having the 1,2-benzanthracene ring system is the 2,3-isomer VII. The alternate structures derivable from 9,10-dihydroretene are 3,4- and 5,6-benzoretene, both of which contain the 3,4-benzphenanthrene ring system. Since the ultraviolet absorption spectrum of 3,4-benzphenanthrene[10] is entirely different from that of 1,2-benzanthracene, the spectrographic data provide conclusive evidence that the new hydrocarbon is 10-methyl-3′-isopropyl-1,2-benzanthracene (VII). The product of succinoylation must then be either β-(9,10-dihydro-2-retoyl)-propionic acid (III) or the 3-isomer. The former structure is the more probable on the basis of analogy and accords well with the fact that the reduced acid on cyclization gives a single isomer in high yield. Exhaustive oxidation of the keto acid with nitric acid was found to provide an unequivocal basis for distinguishing between the two possibilities, for there was isolated a product identified as prehnitic acid (1,2,3,4-acid). Since this can arise from the 2-acid III but not from the isomeric 3-acid, the substance can be assigned the former structure. An attempted correlation of the present series of compounds with Nyman's acetyl-9,10-dihydroretene[8] was unsuccessful. von Pechmann[11] found that β-benzoylacrylic acid can be converted by alkaline cleavage into acetophenone, and the reaction has been applied recently to esters of β-aroylacrylic and β-bromo-β-aroylpropionic acids.[12] Methyl β-(9,10-dihydro-2-retoyl)-propionate was converted readily into the β-bromo derivative, and this afforded the aroylacrylic acid ester on treatment with sodium acetate in acetic acid solution, but treatment of either the bromo ester or the unsaturated ester with alcoholic alkali under various conditions yielded an acidic product which has the composition of a 9,10-dihydroretene carboxylic acid. The substance melts about 30° lower than the acid obtained by Nyman[8] from his acetyl-9,10-dihydroretene and has not been identified.

The 1,2-benzanthracene derivative VII obtained by the above synthesis was found to correspond closely in melting point and in the melting point of the picrate with the benzoretene synthesized by Adelson and Bogert[4] from retene, and direct comparison with material prepared by their method established the identity of the samples. The keto acid obtained by Adelson and Bogert[4] by the succinoylation of retene therefore must be either the 2- or the 3-derivative. A comparison sample of β-(2-retoyl)-propionic acid (VIII) was obtained in low yield by the dehydrogenation of the above 9,10-dihydride III with palladium charcoal. A better yield (66%) was obtained on dehydrogenating the ester of the re-

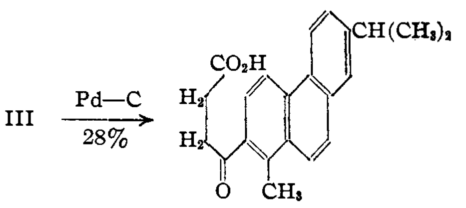
---

[9] R. N. Jones, THIS JOURNAL, 63, 151 (1941).

[10] Mayneord and Roe, *Proc. Roy. Soc.* (London), 158A, 634 (1937).

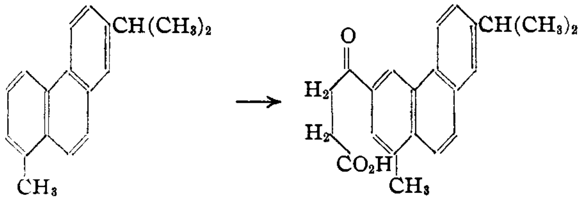
[11] Von Pechmann, *Ber.*, 15, 885 (1882).

[12] Fieser and Hershberg, THIS JOURNAL, 61, 1272 (1939).



VIII

duced acid IV, and the fully aromatized acid was produced by saponification of the ester. The three retene derivatives obtained in this way proved to be different from the corresponding compounds of the Adelson–Bogert series, and it is therefore concluded that the latter compounds are substituted in the 3-position. The succinoylation of retene thus affords the 3-isomer IX as the chief product.



IX

According to a preliminary report cited by Newman and Joshel,[13] the benzoretene of Adelson and Bogert has given no tumors when injected into mice. Since the hydrocarbon has now been identified as 10-methyl-3'-isopropyl-1,2-benzanthracene, it is interesting to note that the high carcinogenic potency of 10-methyl-1,2-benzanthracene is destroyed by the introduction of an isopropyl group into the benz-ring at the 3'-position. It is also of interest that the absence of color distinguishes the hydrocarbon VII from all other known 1,2-benzanthracene derivatives having a methyl group in a meso position.

Experimental Part[14]

9,10-Dihydroretene.[8]—Retene (m. p. 94.5–96°) obtained from the Eastman Kodak Co. gave no test for sulfur and proved satisfactory for hydrogenation; no difference was noted with material purified further by vacuum distillation and crystallization. In a typical experiment 10 g. of retene was hydrogenated without solvent in a steel bomb over 1 g. of copper chromite catalyst (37 KAF) at 160° and an initial pressure of 1250 lb. One mole of gas was absorbed in the course of eight hours, when reaction practically ceased. The solidified reaction product was taken up in alcohol and after clarification with Norit the substance crystallized in the form of large, colorless plates, m. p. 64–65.5°; yield 8.65 g. (86%). A small amount of non-crystalline material was retained in the mother liquor. Purification by vacuum distillation proved less efficacious.

β-(9,10-Dihydro-2-retoyl)-propionic Acid (III).—Sixty-five grams of aluminum chloride was added slowly to a stirred mixture of 50 g. of 9,10-dihydroretene, 21.2 g. of succinic anhydride and 400 cc. of nitrobenzene at 0°. After standing for three hours at 0° and eighteen hours at about 25°, the dark red-brown solution was poured slowly onto 400 g. of ice and 25 cc. of concentrated hydrochloric acid. Steam distillation left a light brown solid which was dissolved in boiling 2% sodium carbonate solution. Acidification of the filtered solution gave 65.8 g. of light tan acid, and on one crystallization from alcohol the substance formed fine, nearly colorless needles, m. p. 156.5–158.5°, dec., yield, 57.1 g. (80%). Two further crystallizations gave colorless material of the constant m. p. 159.2–160°, dec.

Anal. Calcd. for $C_{22}H_{24}O_3$: C, 78.54; H, 7.19. Found: C, 78.62; H, 7.45.

The sodium salt is sparingly soluble in the presence of excess sodium ion and crystallizes readily on cooling the above solution of the acid in 2% carbonate solution in the form of small, lustrous plates. Recrystallization from water gives material very satisfactory for use in the hydrogenation.

The **methyl ester** was prepared by refluxing a solution of 7.18 g. of the acid in 215 cc. of methanol saturated with hydrogen chloride for three hours and pouring the solution into dilute soda solution. Crystallization from methanol yielded 6.5 g. (87%) of material melting at 76–78°. Two further crystallizations gave clusters of colorless plates, m. p. 80.5–81.8°.

Anal. Calcd. for $C_{23}H_{26}O_3$: C, 78.82; H, 7.48. Found: C, 78.75; H, 7.63.

Oxidation of Acid III.—A mixture of 0.45 g. of β-(9,10-dihydro-2-retoyl)-propionic acid, 2 cc. of concentrated nitric acid and 4 cc. of water was heated in a sealed tube at 190–200° for sixteen hours. After opening the tube and adding 2 cc. of concentrated nitric acid, heating was continued for twenty hours, and a second portion (2 cc.) of fresh acid was then added, with further heating for seven hours. Evaporation of the light greenish-yellow solution left a light yellow powder. This was stirred with 6–7 cc. of fuming nitric acid and the undissolved residue was collected and washed well with more acid. The dried product, m. p. 225–230°, dec., was esterified with diazomethane and the ester crystallized from aqueous methanol, giving 0.1 g. of needles, m. p. 117–123°. Two crystallizations from methanol gave silky needles, m. p. 128–129°. A mixture with authentic **prehnitic acid tetramethyl ester** likewise melted at 128–129°.

Methyl β-Bromo-β-(9,10-dihydro-2-retoyl)-propionate.—A solution of 3.5 g. of the methyl ester of acid III in 10 cc. of chloroform was treated at 0° with a few drops of a solution of 1.6 g. of bromine in 5 cc. of chloroform. After a lag of several minutes the reaction started, and the remainder of the bromine solution was then added dropwise and reacted readily. The solvent was removed in vacuum and the residual oil crystallized when rubbed with hexane; yield 3.31 g. (77%), m. p. 85.5–87.5°. Several crystallizations from methanol or hexane yielded colorless plates, m. p. 89.5–90.5°.

---

(13) Newman and Joshel, THIS JOURNAL, **62**, 972 (1940).

(14) All melting points are corrected.

Anal. Calcd. for $C_{23}H_{25}O_3Br$: C, 64.34; H, 5.87. Found: C, 64.22; H, 6.01.

Methyl β-(9,10-Dihydro-2-retoyl)-acrylate.—A solution of 1.95 g. of the bromo ester and 0.8 g. of fused sodium acetate was heated on the steam-bath for one and one-half hours and the yellow solution was poured into water, precipitating a gummy, yellow solid. Crystallization from methanol gave 1.5 g. of material melting at 75–95° and consisting of yellow crystals containing some white solid (unchanged starting material?). Four recrystallizations yielded 0.55 g. (35%) of small yellow plates, m. p. 104–106.5°; after a further crystallization the m. p. was 105–106.3°.

Anal. Calcd. for $C_{23}H_{24}O_3$: C, 79.28; H, 6.94. Found: C, 78.96; H, 6.96.

Action of Alkali on the Bromo Ester and the Unsaturated Ester.—In a typical experiment 1.5 g. of the bromo ester was stirred into a suspension with 15 cc. of alcohol and 9 cc. of 20% aqueous sodium hydroxide was added in portions. The solid rapidly dissolved, with progressive darkening of the solution, and after about twenty minutes a powdery orange precipitate began to separate. After standing at room temperature for six hours the accumulated salt was separated from the red alkaline liquor by filtration, dissolved in water, and the solution acidified. The free acid crystallized from alcohol as clusters of small, light tan plates (0.52 g.), m. p. 192–195°. Two recrystallizations raised the melting point to 199–200.5°, but the dull yellowish color persisted.

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 81.42, 81.51; H, 7.23, 7.39.

Essentially similar results were obtained with the unsaturated ester, and the yield of acid was slightly better. The same reaction product was obtained on refluxing the bromo ester with alcoholic alkali for a brief period. The reaction product was not affected by being refluxed with alcoholic alkali. The mother liquor material from several experiments was examined for the presence of a non-acidic substance, but none was found.

β-(2-Retoyl)-propionic Acid (VIII).—A mixture of 400 mg. of β-(9,10-dihydro-2-retoyl)-propionic acid and 40 mg. of palladium charcoal was heated under nitrogen at 220° for ten minutes and the temperature was then raised to 265° in fifteen minutes (hydrogen evolution 50% of theoretical). Extraction with ether, clarification with Norit, and evaporation gave a yellowish solid. One crystallization from alcohol afforded 110 mg. (28%) of small, colorless plates, m. p. 182–184.5°, dec., and two more crystallizations raised the m. p. to 188.5–190°, dec.

Anal. Calcd. for $C_{22}H_{22}O_3$: C, 79.01; H, 6.63. Found: C, 79.39; H, 6.99.

γ-(9,10-Dihydro-2-retyl)-butyric Acid (IV).—A mixture of 11.04 g. of the sodium salt of the keto acid III, 1.6 g. of copper chromite catalyst, 80 cc. of water and 5 drops of 10% sodium hydroxide was hydrogenated in a steel bomb at 195–200° and an initial pressure of 3000 lb. After ten hours slightly less than two moles of hydrogen had been absorbed. The cooled bomb contained a crystalline sodium salt more soluble than the starting material. It was extracted with hot water and the solution was clarified with Norit and acidified, giving a grayish precipitate. On crystallization from alcohol (Norit) there was obtained 6.83 g. (69%) of product, m. p. 159–160.5°. The recrystallized substance formed colorless plates, m. p. 161.8–162.8°.

Anal. Calcd. for $C_{22}H_{26}O_2$: C, 81.95; H, 8.13. Found: C, 82.07; H, 8.16.

Reduction of the keto acid by the Clemmensen–Martin method[15] proceeded with considerable difficulty, and unchanged starting material was invariably encountered in the reaction mixtures. The keto acid and its reduction product melt at nearly the same temperature and give only a small depression (*ca.* 6°) when mixed.

The **methyl ester** was obtained by Fischer esterification, conducted as above, in 70% yield (m. p. 54–55.2°). The purified substance formed colorless needles from methanol, m. p. 55.5–56.5°.

Anal. Calcd. for $C_{23}H_{28}O_2$: C, 82.10; H, 8.39. Found: C, 81.93; H, 8.30.

Methyl γ-(2-Retyl)-butyrate.—A test-tube containing 380 mg. of methyl γ-(9,10-dihydro-2-retyl)-butyrate and 38 mg. of palladium charcoal was flushed with nitrogen and heated in a bath maintained at 220–265° for fifty minutes and at 265–275° for forty-five minutes (80% of theoretical gas evolution). Extraction with ether (Norit) and crystallization from methanol yielded 250 mg. (66%) of colorless plates, m. p. 79–81°, and the recrystallized sample melted at 81–81.8°.

Anal. Calcd. for $C_{23}H_{26}O_2$: C, 82.59; H, 7.84. Found: C, 82.36; H, 7.96.

γ-(2-Retyl)-butyric Acid.—This was obtained by refluxing the ester (150 mg.) with 1 *N* alcoholic potassium hydroxide, diluting with water and acidifying. The precipitated acid (80 mg., m. p. 196–198°) crystallized from alcohol in lustrous plates, m. p. 197.8–198.6°.

Anal. Calcd. for $C_{22}H_{24}O_2$: C, 82.46; H, 7.55. Found: C, 82.56; H, 7.55.

10-Methyl-3′-isopropyl-8-keto-3,4,5,6,7,8-hexahydro-1,2-benzanthracene (V).—In a typical experiment 6 g. of γ-(9,10-dihydro-2-retyl)-butyric acid and 115 g. of liquid hydrogen fluoride were mixed in a platinum vessel and allowed to stand for five hours and the dull red solution was poured with stirring into ice and water. The gummy solid was taken up in ether and the solution was washed with soda, dried and evaporated. The product crystallized from ligroin (70–90°) as large, yellowish, leafy plates, m. p. 129–130.5°; yield 5.24 g. (92.5%). Two recrystallizations gave colorless plates, m. p. 133.8–134.8°.

Anal. Calcd. for $C_{22}H_{24}O$: C, 86.80; H, 7.95. Found: C, 86.83; H, 8.17.

10-Methyl-3′-isopropyl-3,4,5,6,7,8-hexahydro-1,2-benzanthracene (VI).—High pressure hydrogenation of the ketone V (1.84 g.) in absolute alcohol (10 cc.) over copper chromite catalyst (0.18 g.) in a glass liner proceeded to an apparent end-point at 160° in about three hours. The cloudy solution was diluted with more alcohol, treated with Norit, filtered and concentrated. Once seed was available the hydrocarbon crystallized readily, if slowly, giving 0.9 g. (51%) of material, m. p. 43–45°; the mother liquor afforded only oils. Seed was first ob-

---

(15) Martin, THIS JOURNAL, **58**, 1443 (1936).

tained by distilling the reaction mixture at about 250° (2 mm.) and allowing an alcoholic solution of the viscous distillate to stand for some time at 5°. Some decomposition appears to occur during distillation, however, and purification by crystallization is preferable. The recrystallized substance formed very small, colorless, prismatic plates, m. p. 44.8–46°.

Anal. Calcd. for $C_{22}H_{26}$: C, 90.97; H, 9.02. Found: C, 91.31; H, 8.87.

10-Methyl-3′-isopropyl-1,2-benzanthracene (VII).—A mixture of 0.4 g. of the hexahydride VI and 40 mg. of palladium charcoal was heated under nitrogen in a bath initially at 220°. The temperature was raised to 265° in one hour and then kept at 265–275° for one and one-half hours and at 295–300° for twenty minutes, when gas evolution had ceased. The product, collected by ether extraction and crystallized once from alcohol, was obtained as a crystallizate amounting to 0.34 g. (87%). This consisted in a mixture of plates and needles and melted initially at 82–85° and then, after solidification, at 93–96°. Apparently an unstable polymorphic form was present, but all subsequent crystallizations, effected more slowly, gave only the higher melting form. This separated as long, flat, lustrous needles, m. p. 98–99°. The substance is completely colorless and shows light blue fluorescence in ultraviolet light.

Anal. Calcd. for $C_{22}H_{20}$: C, 92.91; H, 7.09. Found: C, 92.70; H, 7.28.

The **picrate** formed dull red needles from alcohol, m. p. 143.8–144.5°, and showed a tendency to decompose when recrystallized from this solvent. The **trinitrobenzene derivative** crystallized from alcohol in fine, bright orange needles, m. p. 155.8–156.5°.

Synthesis of VII from Retene by the Method of Adelson and Bogert.[4]—Certain variations in procedure were tried in conducting this synthesis. The use of nitrobenzene in place of benzene[4] as the solvent for the succinoylation of retene appears disadvantageous, for under the conditions described for the dihydride we obtained **β-(3-retoyl)-propionic acid** (IX), m. p. 196–198°, dec., in only 21% yield (compare 58.5%[4]). The recrystallized acid melted at 198–199.5°, dec., and gave a depression when mixed with the 2-retoyl isomer. A crystallizate from the mother liquor showed little change in melting point range (*ca.* 170–185°) after six crystallizations. Clemmensen reduction of the keto acid by the acetic acid procedure of Adelson and Bogert[4] proceeded as they describe, and we had no more success than these investigators in attempting to apply the Martin procedure.[15] For cyclization, 5 g. of partially purified γ-(3-retyl)-butyric acid, m. p. 165–170°, was treated with 100 g. of liquid hydrogen fluoride at room temperature for four and one-half hours. One crystallization of the collected neutral product from alcohol gave 2.56 g. (54%) of **10-methyl-3′-isopropyl-5-keto-5,6,7,8-tetrahydro-1,2-benzanthracene**[4] in the form of large, irregular plates, m. p. 136–138°; two recrystallizations, m. p. 139.3–140.3°. A small quantity of oily material separating from the first mother liquor slowly hardened, and on three crystallizations from alcohol afforded 10 mg. of small, slightly yellowish needles, m. p. 132–133.5°. A mixture of this substance with V melted below 118°.

Reduction of the ketone (1 g.) was accomplished by hydrogenation over copper chromite catalyst in alcohol at 160°. Since the viscous concentrate did not crystallize readily it was dehydrogenated with palladium charcoal essentially as described above. The yield of once crystallized **10-methyl-3′-isopropyl-1,2-benzanthracene**, m. p. 95–97°, was 0.58 g. (62% from the ketone). The recrystallized material melted at 98–99° and gave no depression when mixed with the above sample. The picric acid and trinitrobenzene derivatives had the properties described above and mixed melting point determinations indicated no differences.

Summary

9,10-Dihydroretene condenses smoothly with succinic anhydride to give β-(9,10-dihydro-2-retoyl)-propionic acid, which provides a convenient intermediate for the synthesis in good yield of a hydrocarbon characterized as 2,3-benzoretene, or 10-methyl-3′-isopropyl-1,2-benzanthracene, by absorption spectroscopy. The keto acid is shown to be the 2- rather than the 3-derivative by oxidation to prehnitic acid. The aromatic hydrocarbon is identical with the benzoretene synthesized by Adelson and Bogert from the keto acid resulting from the succinoylation of retene. This keto acid is not identical with β-(2-retoyl)-propionic acid, obtained by the dehydrogenation of its 9,10-dihydride, and is therefore assigned the structure of β-(3-retoyl)-propionic acid. The chief point of attack in the succinoylation of retene is thus the same as in other substitutions, as shown by Campbell and Todd.

CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASSACHUSETTS

RECEIVED NOVEMBER 8, 1940