[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

Investigations in the Retene Field. IX. The Synthesis of 5,6-Benzoretene and Some of its Derivatives[1]

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To date, the majority of the polycyclic hydrocarbons which have been shown to possess carcinogenic properties have been pentacyclic or have consisted of four rings containing one or two alkyl substituents. Considering the polynuclear hydrocarbons possessing four rings, it will be recalled that 3,4-benzophenanthrene,[3,4] the simplest carcinogenic substance yet encountered, possesses considerable carcinogenic activity.[5] Turning now to the tetracyclic hydrocarbons containing one or two alkyl groups and exhibiting carcinogenic activity, it has been found that these alkyl homologs are frequently more potent than the parent hydrocarbons. Thus, while 1,2-benzanthracene itself is practically inactive, it acquires cancer-producing properties when alkyl groups are introduced at C_5 and C_6.[5-7] More recently it has been shown that 5,10-dimethyl-1,2-benzanthracene and 10-methyl-1,2-benzanthracene are strongly carcinogenic.[8]

It therefore seemed to us a matter of considerable interest to prepare a benzoretene that would combine both of the features discussed above. 5,6-Benzoretene (VI) possesses the essential tetracyclic structure exhibited by 3,4-benzophenanthrene. Being a 1-methyl-7-isopropyl-5,6-benzophenanthrene, 5,6-benzoretene is of further significance because of the two alkyl groups it carries, two radicals which are frequently found associated in natural products and which seem to have some definite function in nature.

5,6-Benzoretene (VI) is the first benzophenanthrene to be synthesized directly from the parent tricyclic hydrocarbon itself. Other benzophenanthrenes, namely, 3,4-benzophenanthrene,[3,4] 2-methyl-3,4-benzophenanthrene[4] and 6,7-dimethyl-3,4-benzophenanthrene[9] have been derived from simpler substances. In Cook's synthesis of 3,4-benzophenanthrene the formation of a ring system by a Pschorr reaction is accompanied by considerable cyclization to the benzanthracene structure in spite of the fact that the latter requires ring closure at a β-position of the naphthalene system of a molecule in which a free α-position is also available for ring closure. Although Hewett's synthesis gives excellent yields of 3,4-benzophenanthrene and 2-methyl-3,4-benzophenanthrene, its stages are somewhat numerous and lengthy. The diene synthesis of 6,7-dimethyl-3,4-benzophenanthrene employed by L. F. Fieser, M. Fieser and Hershberg has given poor yields of the desired material. While our synthesis of 5,6-benzoretene involves standard reactions, we have been more fortunate with our results. The steps are few and well defined, and the yields are good. Furthermore, since the side chain involved in the ring closure to the tetracyclic compound is at C_6, and since C_7 is occupied by the isopropyl group, only one mode of cyclization is possible, namely, that involving C_5.

Retene (I) and succinic anhydride condensed in benzene solution in the presence of aluminum chloride to give β-6-retoylpropionic acid (III), the orientation of which was shown by oxidation to the known 6-retenecarboxylic acid[10,11] and by its preparation from 6-ω-bromoacetylretene (II) through the agency of the malonic ester synthesis. 6-ω-Bromoacetylretene was formed, together with a small amount of 6-ω-dibromoacetylretene, by bromination of 6-acetylretene.[10] Oxidation of these bromo ketones yielded 6-retenecarboxylic acid[10,11] exclusively, proving that no nuclear bromination had taken place.

We have found that the Friedel and Crafts reactions reported in this paper proceed smoothly in benzene solution without the formation of resinous by-products. This solvent was also found to be excellent in the cyclization experiment carried out in the present project and in a previous one.[12] In passing, it is noteworthy to

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[1] Presented in abstract before the Division of Organic Chemistry, at the Chapel Hill (N. C.) Meeting of the American Chemical Society, April 13, 1937.

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[3] Cook, *J. Chem. Soc.*, 2524 (1931).

[4] Hewett, *ibid.*, 596 (1936).

[5] Barry, Cook, Haslewood, Hewett, Hieger and Kennaway, *Proc. Roy. Soc.* (London), **B117**, 318 (1935).

[6] Cook, *ibid.*, **B111**, 486 (1932).

[7] Barry and Cook, *Am. J. Cancer*, **20**, 58 (1934).

[8] (a) Fieser and Newman, THIS JOURNAL, **58**, 2376 (1936); (b) Fieser and Hershberg, *ibid.*, **59**, 394, 1028 (1937).

[9] L. F. Fieser, M. Fieser and Hershberg, *ibid.*, **58**, 1463 (1936).

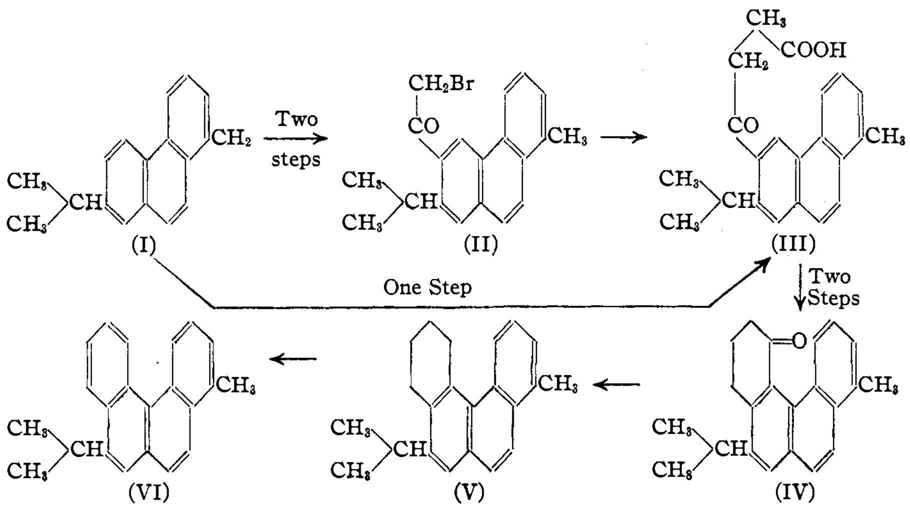
[10] Adelson and Bogert, *ibid.*, **58**, 653 (1936).

[11] Bogert and Hasselstrom, *Proc. Natl. Acad. Sci.*, **18**, 417 (1932).

[12] Adelson and Bogert, THIS JOURNAL, **59**, 399 (1937).

call attention to the fact that to date all of the Friedel and Crafts reactions involving retene have introduced the entering group at C_6.

β-6-Retoylpropionic acid (III) was reduced by the modified Clemmensen method[13] to γ-6-retylbutyric acid which was cyclized to 1'-keto-1',2',3',4'-tetrahydro-5,6-benzoretene (IV) by means of stannic chloride or by the action of aluminum chloride on its acid chloride. The semicarbazone of this cyclic ketone underwent the Wolff reduction[14] to yield 1',2',3',4'-tetrahydro-5,6-benzoretene (V) which was smoothly dehydrogenated by means of sulfur to 5,6-benzoretene (VI). The picrate of 1',2',3',4'-tetrahydro-5,6-benzoretene was found to be stable, in contrast with its isomer, the picrate of 3'-methyl-5,6-cyclopentenoretene,[12] which was readily split into its components on repeated recrystallization.



Preliminary experiments on the Clemmensen reduction of 1'-keto-1',2',3',4'-tetrahydro-5,6-benzoretene (IV) led to a substance which could not be purified. When this reduction product was heated with selenium or with sulfur, copious evolution of hydrogen selenide and hydrogen sulfide, respectively, resulted, but the residual solid yielded no crystalline product. In view of these results it was decided to investigate two alternate routes leading to the same destination, namely, 5,6-benzoretene (VI). Since the desired tetracyclic hydrocarbon (VI) was obtained by the procedure outlined above, these optional syntheses were abandoned at early stages. They are outlined briefly below.

Sodium amalgam reduced the cyclic ketone (IV) to 1'-hydroxyl-1',2',3',4'-tetrahydro-5,6-benzoretene (VII). The remote possibility that hydrogenation took place at C_9 and C_{10} was ruled out by the preparation of its picrate, which proved to be unstable. 9,10-Dihydroretene[15] and 9,10-dihydrophenanthrene[16] do not form picrates.

The second method owes its origin to a synthesis devised by Bougault[17] for the preparation of indenes. This was later adapted by von Auwers and Möller[18] for the closing of six-membered rings. Fieser and Hershberg[19] have employed the von Auwers and Möller adaptation of the Bougault synthesis for the preparation of several types of polycyclic aromatic hydrocarbons. Our procedure was a slight modification of that of Fieser and Hershberg. Methyl γ-6-retylbutyrate (VIII) was condensed with ethyl oxalate in ether solution in the presence of sodium ethylate. The sodium salt of the reaction product was treated with 10% sulfuric acid to yield the free keto ester which was subsequently cyclized by means of 80% sulfuric acid to 3',4'-dihydro-5,6-benzoretene-1',2'-dicarboxylic acid anhydride (IX). Dehydrogenation of the latter with sulfur yielded 5,6-benzoretene-1',2'-dicarboxylic acid anhydride (X). The properties of this aromatic anhydride (X) and its 3',4'-dihydro antecedent (IX) were studied.

In similar fashion to the above-mentioned retene–succinic anhydride synthesis, retene and pyrotartaric anhydride condensed to give α-methyl-β-6-retoylpropionic acid (XI), the configuration of which was established by its synthesis from 6-ω-bromoacetylretene (II) and methylmalonic ester. The normal Clemmensen reduction of this keto acid (XI) failed to change the material; the modified Clemmensen pro-

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(13) Borsche and Rosenkranz, *Ber.*, **52**, 344 (1919).

(14) Wolff, *Ann.*, **394**, 90 (1912).

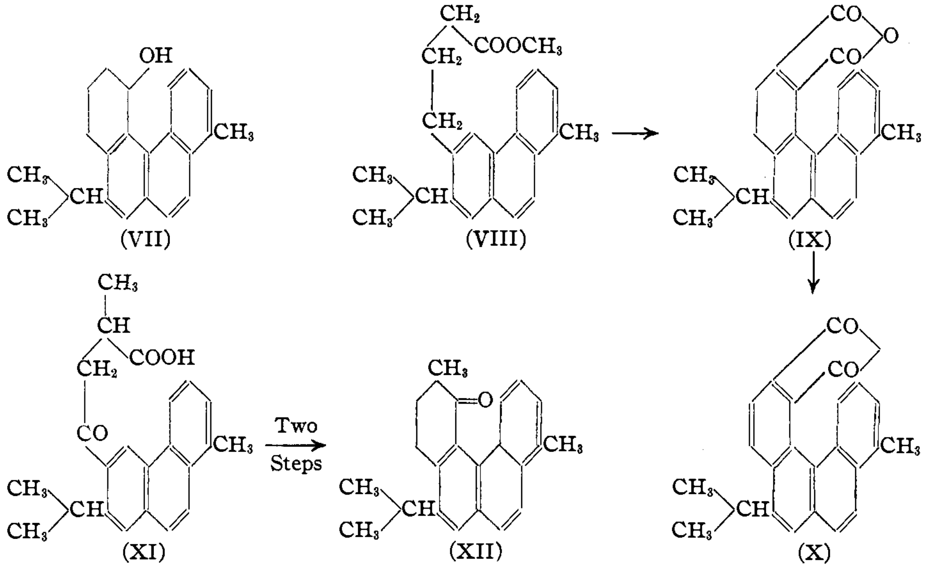
(15) Virtanen, *Ber.*, **53**, 1885 (1920).

(16) (a) Schroeter, *ibid.*, **57**, 2025 (1924); (b) Schroeter, Müller and Huang, *ibid.*, **62**, 645 (1929); (c) Burger and Mosettig, THIS JOURNAL, **58**, 1857 (1936).

(17) Bougault, *Compt. rend.*, **159**, 745 (1915).

(18) Von Auwers and Möller, *J. prakt. Chem.*, **217**, 124 (1925).

(19) Fieser and Hershberg, THIS JOURNAL, **57**, 1508, 1851 (1935).



cedure[13] succeeded with difficulty and then in poor yield. On a small scale this reduction was successful, but when larger quantities were employed, the product was difficult to purify and the yield extremely poor. A somewhat similar phenomenon was noted by Martin[20] in the case of β-*m*-methoxybenzoylpropionic acid. Peculiarly enough, the keto acid (XI) was unaffected when subjected to Martin's modification of the Clemmensen reduction.[20]

The reduction product of the keto acid (XI), α-methyl-γ-6-retylbutyric acid, was cyclized by means of 85% sulfuric acid to 1′-keto-2′-methyl-1′,2′,3′,4′-tetrahydro-5,6-benzoretene (XII). There was insufficient material for further work.

The oestrogenic properties of 5,6-benzoretene-1′,2′-dicarboxylic acid anhydride (X) were investigated by Dr. Earl T. Engle, College of Physicians and Surgeons, Columbia University. The compound was injected subcutaneously in sesame oil solution in a large series of spayed rats in doses varying from 0.1 to 2 mg. It had no oestrogenic activity within that range.

5,6-Benzoretene, 5,6-benzoretene-1′,2′-dicarboxylic acid anhydride and 3′-methyl-5,6-cyclopentenoretene[12] are being studied for carcinogenic activity. The results will be reported at an early date.

Acknowledgments.—Our thanks are due to the Hooker Electrochemical Company, Niagara Falls, N. Y., for a supply of anhydrous aluminum chloride and to the United States Industrial Alcohol Company, Baltimore, Md., for a gift of alcohol.

Experimental

6-ω-Bromoacetylretene (II).—To a solution of 10 g. of 6-acetylretene in 200 cc. of absolute ether cooled to about 10°, there was added with shaking a solution of 5.8 g. of bromine in 200 cc. of absolute ether which previously had been cooled to 0°. Decolorization was usually instantaneous and was always complete after three minutes of shaking. After standing for an hour at 0°, the ethereal solution was treated with anhydrous potassium carbonate and allowed to stand overnight. The filtered solution was evaporated, the residue boiled with methanol and the solution filtered from a small amount of solid matter. Upon cooling, the filtrate deposited crystals which, after a second recrystallization from methanol, appeared as clusters of white needles, m. p. 98.5–99° (corr.); yield, 6.5 g.

Anal. Calcd. for $C_{20}H_{19}OBr$: C, 67.59; H, 5.39. Found: C, 67.48; H, 5.32.

6-ω-Bromoacetylretene (1 g.) was dissolved in a mixture of 50 cc. of dioxane and 10 cc. of 10% sodium hydroxide solution and was oxidized by means of an iodine–potassium iodide solution as previously described for 6-acetylretene.[10] The 6-retenecarboxylic acid thus formed melted at 238–238.5° (corr.) and gave no melting point depression when mixed with an authentic specimen of melting point 238–238.5° (corr.).

6-ω-Dibromoacetylretene.—The insoluble solid from the first methanol recrystallization of 6-ω-bromoacetylretene was boiled with a relatively large volume of methanol and the solution filtered. Upon cooling, the solution deposited small, glistening, cream-colored plates, m. p. 157.5–158° (corr.); yield, 0.25 g. to 0.50 g.

Anal. Calcd. for $C_{20}H_{18}OBr_2$: C, 55.30; H, 4.18. Found: C, 55.33; H, 4.05.

When oxidized by alkaline iodine–potassium iodide solution as described above for 6-ω-bromoacetylretene,

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[20] Martin, This Journal, **58**, 1438 (1936).

6-ω-dibromoacetylretene yielded exclusively 6-retenecarboxylic acid, which was identified by its melting point and mixed melting point with an authentic specimen (both values, 238–238.5° (corr.)).

β-6-Retoylpropionic Acid (III). (a) From 6-ω-Bromoacetylretene.—Sodium (1.1 g.) was powdered under 40 cc. of xylene[21] contained in a 500-cc. three-necked round-bottomed flask fitted with a mechanical stirrer, a dropping funnel and a reflux condenser surmounted by a calcium chloride tube. The xylene was removed by decantation, 35 cc. of dry benzene and 10.8 g. of malonic ester were added to the flask and stirring was started. Sodiomalonic ester formed instantly, appearing as a white, gelatinous mass. To the well-stirred suspension there was added dropwise a solution of 12 g. of 6-ω-bromoacetylretene in 60 cc. of dry benzene and the resulting mixture was stirred and refluxed for ten hours. After cooling, the solution was agitated with 50 cc. of water, 50 cc. of 10% sulfuric acid was added and the benzene and unreacted malonic ester were removed by steam distillation. The viscous red oil that remained was taken up in ether, the solution washed, dried over anhydrous magnesium sulfate and then evaporated. The residue was dissolved in 125 cc. of methanol containing 15 g. of potassium hydroxide and the resulting solution was refluxed for six hours. Most of the methanol was removed in a current of air, hot water was added and the solution was filtered and acidified. The dibasic acid thus precipitated was filtered off and heated in an oil-bath at 185–190° for one hour. The residue dissolved completely in 5% potassium carbonate solution, but the β-6-retoylpropionic acid precipitated by acidification was brown and could not be decolorized by norite treatment. It was dissolved in 30 cc. of hot, concentrated ammonium hydroxide, boiled with norite and filtered. The white ammonium salt that deposited on cooling was filtered, converted to the free acid by acidification with 10% sulfuric acid and the organic acid was dried at 110°. Recrystallized from acetic acid, β-6-retoylpropionic acid appeared as tufts of short, white needles, m. p. 201–202° (corr.); yield, 6 g. Both the acid and its methyl ester (see below) were identical with samples prepared in method (b).

(b) **From Retene.**—To a solution of 23.4 g. of retene in 100 cc. of dry benzene contained in a 500-cc. three-necked round-bottomed flask fitted with an efficient stirrer and a reflux condenser surmounted by a calcium chloride tube, there was added 10 g. of succinic anhydride and, with stirring, 27 g. of anhydrous, powdered aluminum chloride. After stirring for one-half hour at room temperature, the mixture was stirred and refluxed for one and one-half hours, cooled and poured onto a mixture of 200 g. of cracked ice and 10 cc. of concentrated hydrochloric acid contained in a 1-liter round-bottomed flask. After removal of the benzene by steam distillation, the residual suspension was poured into a beaker, the supernatant liquid decanted, the lumpy residue washed by decantation with hot water and a solution of 25 g. of potassium carbonate in 1.5 liters of water was added. The suspension was boiled until all of the lumpy material had gone into solution and only 1–2 g. of amorphous material remained undissolved, filtered and the filtrate acidified. The organic acid thus precipitated was washed by decantation with water, air-dried and recrystallized from acetic acid, from which it appeared as tufts of short, white needles, m. p. 194–196° (corr.); yield 19.5 g. The material was pure enough for subsequent synthetic work. Another recrystallization yielded 16 g. of the β-6-retoylpropionic acid which melted at 201–202° (corr.), not depressed when mixed with a sample of the acid obtained from the malonic ester—6-ω-bromoacetylretene synthesis.

Anal. Calcd. for $C_{22}H_{22}O_3$: C, 79.00; H, 6.64. Found: C, 78.75; H, 6.68.

A mixture of 2 g. of β-6-retoylpropionic acid and 100 cc. of 5% sodium hypochlorite solution containing 2 g. of potassium hydroxide was refluxed gently for six hours, 150 cc. of hot water added and the solution filtered. Acidification yielded a brown solid which was filtered, boiled with 5% potassium hydroxide solution (norite), filtered, reprecipitated by 10% sulfuric acid, dried at 110° and recrystallized from benzene, from which it appeared as small, white needles, m. p. 238–238.5° (corr.); yield 0.5 g. Mixed with an authentic specimen of 6-retenecarboxylic acid of m. p. 238–238.5° (corr.), it showed no depression.

A mixture of 0.3 g. of the 6-retenecarboxylic acid obtained in this oxidation, 0.3 cc. of concentrated sulfuric acid and 15 cc. of methanol was refluxed for five hours, most of the solvent removed in a current of air and the crystalline residue recrystallized from 95% ethanol, from which it appeared as clusters of white needles, m. p. 93–94° (corr.); yield 0.2 g. Mixed with an equal amount of an authentic specimen of methyl 6-retenecarboxylate of m. p. 93–94° (corr.), prepared in similar fashion from a known sample of 6-retenecarboxylic acid, it melted at 93–94° (corr.).

Methyl β-6-Retoylpropionate.—A mixture of 3 g. of β-6-retoylpropionic acid, 3 cc. of concentrated sulfuric acid and 60 cc. of methanol was refluxed for five hours. Upon cooling, the ester crystallized in practically quantitative yield. From methanol, methyl β-6-retoylpropionate appeared as glistening, white plates, m. p. 108–109° (corr.). Mixed with a sample of the ester made from the keto acid obtained in the malonic ester—6-ω-bromoacetylretene synthesis—it showed no depression.

Anal. Calcd. for $C_{23}H_{24}O_3$: C, 79.27; H, 6.95. Found: C, 78.98; H, 6.95.

Oxime of the Methyl Ester.—A suspension of 1 g. of the above methyl ester, 1.5 g. of hydroxylamine hydrochloride and 2 g. of anhydrous barium carbonate in 50 cc. of absolute methanol was refluxed for eight hours, filtered and the filtrate diluted with water. This precipitated the oxime in nearly theoretical yield. Recrystallized from an ethanol-water mixture and then from a mixture of benzene and petroleum ether, the oxime of methyl β-6-retoylpropionate appeared as clusters of small, white plates, m. p. 126–127° (corr.).

Anal. Calcd. for $C_{23}H_{25}O_3N$: C, 75.99; H, 6.94. Found: C, 75.90; H, 6.85.

γ-6-Retylbutyric Acid.—A mixture of 25 g. of β-6-retoylpropionic acid, 150 g. of amalgamated zinc, 350 cc. of acetic acid and 100 cc. of concentrated hydrochloric

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[21] "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, 1932, p. 246.

acid was refluxed for twenty-four hours, an additional 25 cc. of concentrated hydrochloric acid being added after twelve hours. The hot solution was decanted from the unreacted zinc, 50 cc. of hot water added, and the resulting solution allowed to cool. The solid thus deposited was filtered and recrystallized twice from acetic acid, from which it appeared as small, white plates, m. p. 174–176° (corr.); yield 14 g. The material was sufficiently pure for subsequent synthetic work. Further recrystallization raised the melting point of γ-6-retylbutyric acid to 179–179.5° (corr.) where it remained constant.

Anal. Calcd. for $C_{22}H_{24}O_2$: C, 82.45; H, 7.56. Found: C, 82.55, 82.61; H, 7.53, 7.73.

Methyl γ-6-Retylbutyrate.—This was prepared in the usual manner by refluxing a mixture of 7 g. of γ-6-retylbutyric acid, 5 cc. of concentrated sulfuric acid and 100 cc. of methanol for five hours. Recrystallized from methanol, methyl γ-6-retylbutyrate appeared as small, white plates, m. p. 66.5–67.5° (corr.); yield 6 g.

Anal. Calcd. for $C_{23}H_{26}O_2$: C, 82.58; H, 7.84. Found: C, 82.70; H, 7.91.

1'-Keto-1',2,'3',4'-tetrahydro-5,6-benzoretene (IV).—(a) A mixture of 9.2 g. of γ-6-retylbutyric acid, 6 g. of powdered phosphorus pentachloride and 75 cc. of dry benzene was stirred and refluxed for one hour, cooled and 5.8 g. of anhydrous, powdered aluminum chloride was added in portions with stirring. The resulting mixture was stirred for one-half hour at room temperature, then for two and one-half hours at gentle reflux, cooled and poured onto cracked ice containing some concentrated hydrochloric acid. The benzene was removed by steam distillation and the viscous solid that remained behind was extracted with 300 cc. of 3% potassium hydroxide solution. Acidification of the alkaline filtrate yielded 3 g. of unchanged γ-6-retylbutyric acid. The alkali-insoluble residue was recrystallized from *n*-propanol, from which it appeared as glistening white plates, m. p. 139.5–140° (corr.); yield 3 g.

(b) Five grams of γ-6-retylbutyric acid and 12 cc. of anhydrous stannic chloride were heated at 105–110° for one and one-half hours. After cooling, the viscous residue was dissolved in cold acetone and the solution poured onto cracked ice containing some concentrated hydrochloric acid. The solid thus formed was extracted with 400 cc. of 3% potassium hydroxide solution. The alkali-insoluble residue, 1'-keto-1',2',3',4'-tetrahydro-5,6-benzoretene, appeared from *n*-propanol as glistening, white plates, m. p. 139.5–140° (corr.); yield 2.3 g.

Anal. Calcd. for $C_{22}H_{22}O$: C, 87.37; H, 7.34. Found: C, 87.23; H, 7.27.

Oxime.—This was prepared as described above for the oxime of methyl β-6-retoylpropionate. Recrystallized from benzene, the oxime of 1'-keto-1',2',3',4'-tetrahydro-5,6-benzoretene appeared as small, white plates, m. p. 203–204° (corr.), with decomposition; yield, practically that calculated.

Anal. Calcd. for $C_{22}H_{23}ON$: C, 83.23; H, 7.31; N, 4.42. Found: C, 83.45; H, 7.05; N, 4.68.

Semicarbazone.—A suspension of 2 g. of 1'-keto-1',2',3',4'-tetrahydro-5,6-benzoretene, 4 g. of semicarbazide hydrochloride and 5 g. of anhydrous barium carbonate in 50 cc. of absolute ethanol was refluxed for eight hours, filtered and the filtrate diluted with water. This precipitated part of the semicarbazone which was then recrystallized from benzene. The remainder of the semicarbazone, which was only slightly soluble in ethanol, was obtained by extracting the solid residue from the above filtration with benzene and concentrating the benzene extract. The semicarbazone of 1'-keto-1',2',3',4'-tetrahydro-5,6-benzoretene appeared as microscopic, white crystals which melted with decomposition at 242–244° (corr.); yield 1.4 g.

Anal. Calcd. for $C_{23}H_{25}ON_3$: C, 76.84; H, 7.02; N, 11.70. Found: C, 77.11; H, 7.40; N, 11.59.

1',2',3',4'-Tetrahydro-5,6-benzoretene (V).—A mixture of 1.300 g. of the above semicarbazone, 0.80 g. of sodium and 10 cc. of absolute ethanol was heated in a sealed tube at 190–200° for twenty-four hours. After cooling and opening the tube, its contents were washed into a separatory funnel with benzene followed by water. The benzene layer was washed thoroughly and evaporated. 1',2',3',4'-Tetrahydro-5,6-benzoretene appeared from absolute ethanol as large, white prisms, m. p. 88–89° (corr.); yield 0.740 g.

Anal. Calcd. for $C_{22}H_{24}$: C, 91.61; H, 8.39. Found: C, 91.67; H, 8.24.

Picrate.—This was made by mixing hot solutions of 0.194 g. of the pure hydrocarbon and 0.162 g. of picric acid, each in 4 cc. of absolute ethanol and boiling for five minutes. The picrate crystallized out in quantitative yield on cooling. Recrystallized from absolute ethanol, the picrate of 1',2',3',4'-tetrahydro-5,6-benzoretene appeared as bright orange needles, m. p. 159–160° (corr.), which was quite stable and did not split into its components on repeated recrystallization.

Anal. Calcd. for $C_{28}H_{27}O_7N_3$: C, 64.96; H, 5.26; N, 8.13. Found: C, 65.23; H, 5.26; N, 8.18.

5,6-Benzoretene (VI).—A mixture of 0.400 g. of 1',2',3',4'-tetrahydro-5,6-benzoretene and 0.090 g. of sulfur was heated one hour and fifteen minutes at 220–230°. After cooling, the reaction mass was taken up in 4 cc. of benzene, boiled for five minutes with a solution of 0.40 g. of picric acid in 2 cc. of benzene and cooled. The crystalline picrate of 5,6-benzoretene thus obtained was recrystallized three times from *n*-propanol, from which it appeared as clusters of short, dark red needles, m. p. 144–144.5° (corr.); yield 0.380 g. A portion was removed for analysis and the remainder treated as noted below.

Anal. Calcd. for $C_{28}H_{23}O_7N_3$: C, 65.47; H, 4.52; N, 8.19. Found: C, 65.64; H, 4.43; N, 8.34.

The hydrocarbon was recovered by distribution of the picrate between a dilute ammonium hydroxide solution (1:3 by vol.) and benzene. Recrystallized from a *n*-propanol–water mixture, 5,6-benzoretene appeared as long, silky white needles, m. p. 98–99° (corr.); yield 0.155 g.

Anal. Calcd. for $C_{22}H_{20}$: C, 92.91; H, 7.09. Found: C, 93.11; H, 7.13.

1'-Hydroxy-1', 2', 3', 4'-tetrahydro-5, 6-benzoretene (VII).—A mixture of 0.5 g. of 1'-keto-1',2',3',4'-tetrahydro-5,6-benzoretene, 9 g. of a 3% sodium amalgam and 10 cc. of ethanol was refluxed for six hours, allowed to stand overnight and filtered. Dilution of the filtrate followed by acidification yielded a pale brown solid. Recrystallized from methanol (norite), 1′-hydroxy-1′,2′,3′,4′-tetrahydro-5,6-benzoretene appeared as glistening white flakes, m. p. 131–132° (corr.); yield 0.250 g. A mixture with an equal amount of the starting cyclic ketone (IV) of m. p. 139.5–140° (corr.) melted at 98–106° (corr.).

Anal. Calcd. for $C_{22}H_{24}O$: C, 86.79; H, 7.95. Found: C, 86.59; H, 8.23.

Picrate.—This was prepared as described above from 0.200 g. of the pure hydroxy compound and 0.159 g. of picric acid each in 4 cc. of absolute ethanol. Recrystallized from absolute ethanol, it appeared as pale orange needles, m. p. 154.5–155° (corr.); yield, practically that calculated. The picrate of 1′-hydroxy-1′,2′,3′,4′-tetrahydro-5,6-benzoretene was readily split into its components on repeated recrystallization, the parent hydroxy compound crystallizing out with the picrate.

Anal. Calcd. for $C_{28}H_{27}O_8N_3$: C, 63.01; H, 5.10; N, 7.88. Found: C, 64.06; H, 5.25; N, 7.48.

3′,4′-Dihydro-5,6-benzoretene-1′,2′-dicarboxylic Acid Anhydride (IX).—Sodium (0.90 g.) was dissolved in 25 cc. of absolute ethanol and the solution heated in an oil-bath until the temperature of the latter was 180°. After thorough cooling, the residual sodium ethylate was treated with 6.4 g. of ethyl oxalate and 9.5 g. of methyl γ-6-retylbutyrate in 75 cc. of absolute ether and the whole refluxed for twenty-four hours. Toward the end of this period the sodium salt of the condensation product began to precipitate. The ethereal suspension was transferred to a separatory funnel, shaken with 10% sulfuric acid, the ethereal layer separated and evaporated. The resulting oil was heated with 125 cc. of 80% sulfuric acid for one hour on the steam-bath, cooled and cracked ice was added. The product of this cyclization, 3′,4′-dihydro-5,6-benzoretene-1′,2′-dicarboxylic acid anhydride, was obtained by filtration followed by washing with a small amount of cold ethanol, then ether. Recrystallized from acetic anhydride, 3′,4′-dihydro-5,6-benzoretene-1′,2′-dicarboxylic acid anhydride appeared as long, bright yellow needles, m. p. 219–220° (corr.); yield 5.5 g.

Anal. Calcd. for $C_{24}H_{20}O_3$: C, 80.86; H, 5.66. Found: C, 80.71; H, 5.51.

The anhydride gave an excellent fluorescein test on fusion with resorcinol and concentrated sulfuric acid.

The anhydride (0.20 g.) was boiled with 15 cc. of methanol containing 0.5 g. of potassium hydroxide, solution taking place rapidly. After cooling and diluting, the solution was acidified carefully and the precipitate thus formed was filtered and recrystallized from benzene, from which it appeared as long, yellow needles, m. p. 218–219° (corr.); yield 0.17 g. Mixed with a sample of 3′,4′-dihydro-5,6-benzoretene-1′,2′-dicarboxylic acid anhydride of melting point 219–220° (corr.), it melted at 218–220° (corr.).

Dimethyl Ester.—A mixture of 0.90 g. of the above anhydride, 0.9 cc. of concentrated sulfuric acid and 30 cc. of methanol was refluxed for ten hours. The solvent was removed, the residue taken up in ether and the solution washed successively with water, 3% potassium hydroxide solution and water. After drying the ethereal solution over anhydrous calcium chloride and removing the solvent, the residual ester was recrystallized from a dioxane–water mixture. From this solvent dimethyl 3′,4′-dihydro-5,6-benzoretene-1′,2′-dicarboxylate appeared as glistening, yellow flakes, m. p. 145.5–146.5° (corr.); yield 0.30 g.

Anal. Calcd. for $C_{26}H_{26}O_4$: C, 77.57; H, 6.51. Found: C, 77.01; H, 6.56.

5,6-Benzoretene-1′,2′-dicarboxylic Acid Anhydride (X).—A mixture of 2.300 g. of 3′,4′-dihydro-5,6-benzoretene-1′,2′-dicarboxylic acid anhydride and 0.210 g. of sulfur was heated with shaking in a nitrate-bath at 230° until the sulfur had dissolved, and the bath temperature was then raised to 240–250° until the evolution of hydrogen sulfide ceased (about twenty-five minutes). The residue was recrystallized from pyridine, from which it appeared as bright orange needles, m. p. 244.5–245.5° (corr.); yield 1.150 g. 5,6-Benzoretene-1′, 2′-dicarboxylic acid anhydride gave an excellent fluorescein test when fused with resorcinol and sulfuric acid.

Anal. Calcd. for $C_{24}H_{18}O_3$: C, 81.32; H, 5.12. Found: C, 81.36; H, 5.43.

5,6-Benzoretene-1′,2′-dicarboxylic Acid.—The anhydride (X) was hydrolyzed as described above for the dihydro anhydride (IX). The precipitate formed in this case upon acidification of the alkaline solution proved to be the dicarboxylic acid. Recrystallized from a dioxane–water mixture, 5,6-benzoretene-1′, 2′-dicarboxylic acid appeared as microscopic, yellow crystals which melted with decomposition at 240–241° (corr.); yield, practically that calculated. When cooled, the melted compound recongealed to a bright orange solid which remelted at 241–243° (corr.); mixed with a sample of 5, 6-benzoretene-1′, 2′-dicarboxylic acid anhydride of melting point 244.5–245.5° (corr.), it showed no depression. When a portion of the dicarboxylic acid was dissolved in hot acetic anhydride, the anhydride (X) crystallized out upon cooling; this was established by its melting point, 242–243° (corr.), and mixed melting point, 242–243° (corr.), with an authentic sample of the anhydride. Attempts to decarboxylate the dipotassium salt of this acid were unsuccessful. The dicarboxylic acid was dried at 110° prior to analysis.

Anal. Calcd. for $C_{24}H_{20}O_4$: C, 77.39; H, 5.42. Found: C, 77.50; H, 5.38.

α-Methyl-β-6-retoylpropionic Acid (XI). (a) From 6-ω-Bromoacetylretene.—This was prepared as described above from 0.7 g. of sodium, 8.4 g. of methylmalonic ester and 7.5 g. of 6-ω-bromoacetylretene in 70 cc. of dry benzene, with the following modifications. Five hours of stirring and refluxing were required for the sodium and the methylmalonic ester to react. The crude acid obtained by decarboxylation of the dibasic acid from the malonic ester synthesis was converted to its sparingly soluble sodium salt by means of 2% sodium carbonate solution. The sodium salt was purified by recrystallization from water and then converted to the free acid. Recrystallized from acetic acid, α-methyl-β-6-retoylpropionic acid appeared as tufts of short, white needles, m. p. 210–211° (corr.); yield 3.8 g.

(b) From Retene.—This was prepared as described above for β-6-retoylpropionic acid from 23.4 g. of retene, 11.4 g. of pyrotartaric anhydride and 27 g. of anhydrous powdered aluminum chloride. Recrystallized from acetic acid, α-methyl-β-6-retoylpropionic acid appeared as tufts of short, white needles, m. p. 210–211° (corr.); yield 10 g. Mixed with a sample of the acid of melting point 210–211° (corr.) obtained in (a), it melted at 210–211° (corr.).

Anal. Calcd. for $C_{23}H_{24}O_3$: C, 79.27; H, 6.95. Found: C, 79.18; H, 7.01.

Methyl Ester.—This was prepared as described for methyl β-6-retoylpropionate from 3 g. of the methyl keto acid (XI), 3 cc. of concentrated sulfuric acid and 75 cc. of methanol. The solution was evaporated to half of its original volume to obtain the ester. Recrystallized from methanol, methyl α-methyl-β-6-retoylpropionate appeared as clusters of white needles, m. p. 96–97° (corr.); yield, practically that calculated. Samples of the ester produced by esterification of the methyl keto acid (XI) from (a) and (b) proved to be identical.

Anal. Calcd. for $C_{24}H_{26}O_3$: C, 79.51; H, 7.24. Found: C, 79.33; H, 7.23.

Oxime of the Methyl Ester.—This was synthesized as described above from 1 g. of the methyl keto ester, 1.5 g. of hydroxylamine hydrochloride and 2 g. of anhydrous barium carbonate in 25 cc. of methanol. Recrystallized from a methanol–water mixture, the oxime of methyl α-methyl-β-6-retoylpropionate appeared as white needles, m. p. 135–135.5° (corr.); yield, practically that calculated.

Anal. Calcd. for $C_{24}H_{27}O_3N$: C, 76.35; H, 7.22. Found: C, 76.32; H, 7.26.

α-Methyl-γ-6-retylbutyric Acid.—Two grams of α-methyl-β-6-retoylpropionic acid, 12 g. of amalgamated zinc and 50 cc. of glacial acetic acid were heated to brisk reflux and five 2-cc. portions of concentrated hydrochloric acid were added over a two-hour period. Refluxing was continued for a total of forty-four hours, an additional 20 cc. of concentrated hydrochloric acid being added in 2-cc. portions at regular intervals. After decanting from the unreacted zinc and cooling, the solution deposited a white solid which was filtered and precipitated once from 3% potassium hydroxide solution. Recrystallized from a petroleum solvent,[22] α-methyl-γ-6-retylbutyric acid appeared as microscopic, white crystals, m. p. 131–132° (corr.); yield 0.6 g.

Anal. Calcd. for $C_{23}H_{26}O_2$: C, 82.58; H, 7.84. Found: C, 82.40, 82.29; H, 7.93, 7.86.

In cold, concentrated sulfuric acid, it dissolved to a blood-red solution, the color of which was discharged by dilution.

1′-Keto-2′-methyl-1′,2′,3′,4′-tetrahydro-5,6-benzoretene (XII).—A mixture of 0.20 g. of α-methyl-γ-6-retylbutyric acid and 2 cc. of 85% sulfuric acid was heated on the steam-bath for fifteen minutes, the resulting crimson solution cooled and poured onto cracked ice. The suspension thus obtained was extracted with ether, the ethereal solution washed with water, 3% potassium hydroxide solution and water and dried over anhydrous calcium chloride. After removal of the solvent and recrystallization from 95% ethanol, 1′-keto-2′-methyl-1′,2′,3′,4′-tetrahydro-5,6-benzoretene appeared as thin, white plates, m. p. 120.5–121.5° (corr.); yield 0.08 g.

Anal. Calcd. for $C_{23}H_{24}O$: C, 87.29; H, 7.65. Found: C, 87.12, 87.10; H, 7.71, 7,89.

Summary

1. A well-defined synthesis of 5,6-benzoretene from retene in six steps has been developed. β-6-Retoylpropionic acid, obtained by the Friedel and Crafts condensation of retene and succinic anhydride, undergoes the Clemmensen reduction to yield γ-6-retylbutyric acid which is cyclized to 1′-keto-1′,2′,3′,4′-tetrahydro-5,6-benzoretene. The latter is reduced to the corresponding tetrahydro compound which is smoothly dehydrogenated by sulfur to 5,6-benzoretene.

2. Several derivatives of 5,6-benzoretene have been prepared, including 1′-hydroxy-1′,2′,3′,4′-tetrahydro-5,6-benzoretene, 5,6-benzoretene-1′,2′-dicarboxylic acid anhydride and 1′-keto-2′-methyl-1′,2′,3′,4′-tetrahydro-5,6-benzoretene.

3. Certain of these new products are being tested for their carcinogenic properties.

NEW YORK, N. Y.

RECEIVED JUNE 24, 1937

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(22) B. p. 77–115°. The solvent gave no coloration when shaken with concentrated sulfuric acid.