[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

Investigations in the Retene Field. VIII. The Synthesis of 3′-Methyl-5,6-cyclopentenoretene

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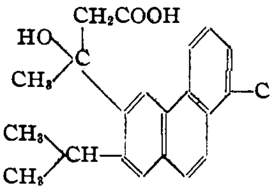
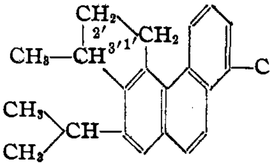
In a preliminary communication[2] announcement was made of the synthesis of 3′-methyl-5,6-cyclopentenoretene using 6-acetylretene[3] as the starting material. At that time attention was called to the fact that such a polycyclic hydrocarbon should be of interest because it arose as a synthetic product of retene, itself a natural product containing methyl and isopropyl groups which apparently have a very significant function in nature. Furthermore, 3′-methyl-5,6-cyclopentenoretene was shown to be of interest because it is a methyl isopropyl homolog of Diels' hydrocarbon[4] which has been the subject of much scientific investigation because of its isolation as a dehydrogenation product of a wide variety of naturally occurring materials.

It is of significance that retene was used for comparative purposes in preliminary work on the structure of Diels' hydrocarbon. Rosenheim and King[5] pointed out the striking similarity between the ultraviolet absorption spectra of Diels' hydrocarbon and retene and cited this fact as conclusive proof that this $C_{18}H_{16}$ was a phenanthrene derivative. Bernal and Crowfoot[6] suggested that Diels' hydrocarbon was a methylcyclopentenophenanthrene because of the striking similarity of the cell dimensions of this $C_{18}H_{16}$ to those of retene.

The Reformatsky reaction between 6-acetylretene, ethyl bromoacetate and zinc dust yielded a hydroxy ester which was hydrolyzed to β-hydroxy-β-6-retylbutanoic acid (I). The latter was further characterized by the preparation of its methyl ester. The hydroxy acid (I) was dehydrated by means of acetic anhydride to β-6-retylcrotonic acid which was then reduced to β-6-retylbutanoic acid. Cyclization of the acid chloride of the latter through the agency of aluminum chloride in benzene solution gave 1′-keto-3′-methyl-5,6-cyclopentenoretene which was characterized by the preparation of its oxime. This cyclic ketone was converted into 3′-methyl-5,6-cyclopentenoretene (II) by means of the Clemmensen reduction.



(I)



(II)

Inasmuch as 6-acetylretene was used as the starting material, the structure of 3′-methyl-5,6-cyclopentenoretene was defined at once. C_7 being occupied by the isopropyl group, only C_5 was available for ring closure. Solutions of 3′-methyl-5,6-cyclopentenoretene exhibited no fluorescence. Hillemann[7] has reported similar findings for three isomeric methylcyclopentenophenanthrenes.

The picrate of 3′-methyl-5,6-cyclopentenoretene was found to be unstable, being readily split into its components on repeated recrystallization. This is similar to the behavior of the picrate of 3′-methyl-1,2-cyclopentenophenanthrene.[8,9,10]

The physiological properties of 3′-methyl-5,6-cyclopentenoretene are being studied and will be reported at an early date.

Acknowledgment.—Our thanks are due to the Hooker Electrochemical Company, Niagara Falls, N. Y., for a generous supply of anhydrous aluminum chloride.

Experimental

β-Hydroxy-β-6-retylbutanoic Acid.—To a solution of 10 g. of 6-acetylretene and 17 g. of ethyl bromoacetate in 40 cc. of dry benzene, there was added 14 g. of zinc dust and a few crystals of iodine and the resulting mixture was carefully heated to the boiling point. After the initial vigorous reaction had subsided somewhat, the mixture was refluxed for three hours, cooled and poured onto a mixture of

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[1] National Research Fellow in Chemistry.

[2] Adelson and Bogert, *Proc. Natl. Acad. Sci.*, **23**, in press (1937).

[3] Adelson and Bogert, THIS JOURNAL, **57**, 653 (1936).

[4] Diels, Gädke and Körding, *Ann.*, **459**, 1 (1927).

[5] Rosenheim and King, *Chemistry and Industry*, **52**, 299 (1933).

[6] Bernal and Crowfoot, *ibid.*, **52**, 729 (1933); *J. Chem. Soc.*, 93 (1935).

[7] Hillemann, *Ber.*, **69**, 2610 (1936).

[8] Harper, Kon and Ruzicka, *J. Chem. Soc.*, 124 (1934).

[9] Gamble, Kon and Saunders, *ibid.*, **644** (1935).

[10] Ruzicka and Thomann, *Helv. Chim. Acta*, **16**, 226 (1933).

cracked ice and 10% sulfuric acid. The benzene layer was separated, washed successively with 10% sulfuric acid, water, 5% sodium carbonate solution and water and the solvent was removed. The brown oil which remained could not be induced to crystallize. It was dissolved in 80 cc. of methanol containing 10 g. of potassium hydroxide and the resulting solution was refluxed for four hours. Most of the methanol was removed in a current of air, water added and the solution acidified. A brown precipitate (11.4 g.) formed. Recrystallized from a mixture of chloroform and petroleum ether (b. p. 40–60°), *β*-hydroxy-*β*-6-retylbutanoic acid appeared as fine, white crystals which melted with decomposition at 118–119° (corr.); yield, 8 g. Further recrystallization raised the melting point to 121–122° (corr.) where it remained constant.

Anal. Calcd. for $C_{22}H_{24}O_3$: C, 78.52; H, 7.20. Found: C, 78.24; H, 7.44.

Methyl Ester.—This was prepared and worked up as described above from 3.5 g. of 6-acetylretene, 6 g. of methyl bromoacetate and 5 g. of zinc dust in 30 cc. of dry benzene. After removal of the benzene, there remained an oil which solidified upon standing to a pale yellow solid; yield, 4 g. From 95% ethanol methyl *β*-hydroxy-*β*-6-retylbutanoate appeared as tiny, pale yellow crystals, m. p. 90–90.5° (corr.).

Anal. Calcd. for $C_{23}H_{26}O_3$: C, 78.81; H, 7.48. Found: C, 78.59; H, 7.32.

***β*-6-Retylcrotonic Acid.**—A mixture of 10 g. of *β*-hydroxy-*β*-6-retylbutanoic acid, 20 g. of anhydrous sodium acetate and 75 cc. of freshly distilled acetic anhydride was refluxed for three hours, cooled and poured into 500 cc. of water. After the acetic anhydride had been destroyed and the aqueous solution removed by decantation, the crude solid was boiled with 400 cc. of 1% potassium hydroxide solution and filtered. Acidification precipitated 9 g. of a pale brown solid. Recrystallized from an ethanol–water mixture (norite), *β*-6-retylcrotonic acid appeared as short, white needles, m. p. 205–206° (corr.) with decomposition; yield, 7 g. An acetone solution of the unsaturated acid decolorized a solution of potassium permanganate in acetone.

Anal. Calcd. for $C_{22}H_{22}O_2$: C, 82.98; H, 6.97. Found: C, 83.25; H, 7.15.

***β*-6-Retylbutanoic Acid.**—Eight grams of *β*-6-retylcrotonic acid was dissolved in 110 cc. of absolute methanol containing 2 g. of potassium hydroxide and 180 g. of 3% sodium amalgam was added. The resulting mixture was refluxed for six hours, allowed to stand overnight and filtered. Dilution of the filtrate followed by acidification yielded 8 g. of solid material. *β*-6-Retylbutanoic acid crystallized from a petroleum solvent[11] as small, glistening white plates, m. p. 152.5–153.5° (corr.); yield, 7 g.

Anal. Calcd. for $C_{22}H_{24}O_2$: C, 82.45; H, 7.56. Found: C, 82.60; H, 7.50.

1′-Keto-3′-methyl-5,6-cyclopentenoretene.—A mixture of 10 g. of *β*-6-retylbutanoic acid, 7 g. of powdered phosphorus pentachloride and 75 cc. of dry benzene was stirred and refluxed for one hour, cooled and 6.7 g. of anhydrous, powdered aluminum chloride was added in portions with stirring. The resulting mixture was stirred one-half hour at room temperature, then 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 350 cc. of 3% potassium carbonate solution. Acidification of the carbonate filtrate yielded 2 g. of unchanged *β*-6-retylbutanoic acid. The carbonate-insoluble residue was dissolved in 75 cc. of *n*-propanol, a hot solution of 7 g. of picric acid in 40 cc. of *n*-propanol was added and the mixture boiled for five minutes. The picrate that separated on cooling was recrystallized twice from 95% ethanol and the keto compound was regenerated by distribution between a 5% sodium carbonate solution and ether; yield, 3 g. Recrystallized from a petroleum solvent[11] and then from 95% ethanol, 1′-keto-3′-methyl-5,6-cyclopentenoretene appeared as short, pale yellow needles, m. p. 111.5–112.5° (corr.).

Anal. Calcd. for $C_{22}H_{22}O$: C, 87.37; H, 7.34. Found: C, 87.08; H, 7.57.

Oxime.—A suspension of 0.4 g. of the above ketene, 0.8 g. of hydroxylamine hydrochloride and 1.2 g. of anhydrous barium carbonate in 25 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 dilute ethanol, it appeared as short, white needles which darkened somewhat at 192° (corr.) and melted with decomposition at 194–195° (corr.).

Anal. Calcd. for $C_{22}H_{23}ON$: C, 83.23; H, 7.31. Found: C, 82.96; H, 7.32.

3′-Methyl-5,6-cyclopentenoretene.—A mixture of 1.6 g. of 1′-keto-3′-methyl-5,6-cyclopentenoretene, 9 g. of amalgamated zinc and 20 cc. of concentrated hydrochloric acid was refluxed for twenty-four hours, an additional 5 cc. of acid being added after twelve hours. The pale yellow oil that resulted was taken up in ether, the ethereal solution washed with 10% hydrochloric acid, water and the solvent evaporated. The residue was dissolved in hot 95% ethanol, a hot solution of 1.9 g. of picric acid in 95% ethanol was added and the resulting picrate was twice recrystallized from absolute ethanol. The hydrocarbon (1 g.) was recovered by distribution of the picrate between a 5% sodium carbonate solution and ether. Recrystallized from an ethanol–water mixture, 3′-methyl-5,6-cyclopentenoretene appeared as short, white needles, m. p. 74.5–75.5° (corr.). The hydrocarbon was soluble in the common organic solvents and in vegetable oils.

Anal. Calcd. for $C_{22}H_{24}$: C, 91.61; H, 8.39. Found: C, 91.52, 91.95; H, 8.68, 8.73.

Picrate.—This was prepared by mixing hot solutions of 0.174 g. of the pure hydrocarbon and 0.146 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, it appeared as bright orange needles, m. p. 154–155° (corr.). The picrate of 3′-methyl-5,6-cyclopentenoretene was readily split into its components on repeated recrystallization.

Anal. Calcd. for $C_{28}H_{27}O_7N_3$: C, 64.96; H, 5.26. Found: C, 64.36; H, 5.43.

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[11] B. p. 77–115°. The solvent gave no coloration when shaken with concentrated sulfuric acid.

Summary

1. Hydrolysis of the product obtained in the Reformatsky reaction between 6-acetylretene and ethyl bromoacetate yields β-hydroxy-β-6-retylbutanoic acid.

2. Dehydration of this acid followed by reduction gives β-6-retylbutanoic acid whose acid chloride yields upon cyclization 1′-keto-3′-methyl-5,6-cyclopentenoretene.

3. The Clemmensen reduction of this cyclic ketone yields 3′-methyl-5,6-cyclopentenoretene.

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A Series of Aliphatic Dimethyl Amides[1]

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Dimethyl amides have been prepared by several investigators,[3] but the data on them are incomplete and not correlated. It seemed desirable to make a complete series of them so that comparisons can be made, not only between individual compounds, but also between this and other series. The eight dimethyl amides of the normal acids from formic to caprylic have been prepared and characterized. An unexpected discovery was that the acids except formic and their dimethyl amides give azeotropes boiling 4–5° *above* the amides. The data are in Table I and II. All of these dimethyl amides are mobile liquids which mix in all proportions with carbon disulfide, chloroform, carbon tetrachloride, benzene, ether, acetone and alcohol. The first two have limited solubility in petroleum ether, while the others mix with it. The lower members mix with water, but the higher homologs become increasingly insoluble; the solubility of VIII in water is less than 1%. In these respects dimethyl amides resemble esters, except that they are much more soluble in water and boil at substantially higher temperatures than esters of the same carbon content.

Another object was to investigate further the method of preparation of dimethyl amides recently proposed by Mitchell and Reid.[4] Repetition of their work showed that dimethyl amides are formed in liberal amounts by their procedure, but that the reactions are not complete, except with formic acid. Fractionation, taking very close cuts, gave what appeared to be pure compounds, but these proved to be azeotropic mixtures of the dimethyl amides and the acids. These azeotropes caused Mitchell and Reid to overestimate their yields and troubled van der Zande.[5] The data on these constant boiling mixtures are brought together in Table II.

Experimental

Two equivalents of gaseous dimethylamine was passed into an acid which was heated under a reflux condenser from the top of which the excess of amine passed to a water trap. The water in the condenser jacket was kept warm enough to permit water vapor to escape. When there seemed to be no further reaction, the product was fractionated through a six-foot (2 meter) precision still,[6] a narrow cut being taken at what appeared to be the boiling point. The products were found to contain free acid which was titrated with the results given in Table II. Several experiments were made with acetic acid, noting the temperature of the boiling mixture, and titrating samples of it after successive portions of amine had been added. No matter how much amine was passed in the liquid in the flask never became neutral.

Dimethyl acetamide was obtained in 78% yield by heating 360 g. of acetic acid, saturated with gaseous dimethylamine at 35°, for five hours at 200° in a steel bomb. Solid caustic potash was added to the product to take up water and acetic acid. The liquid thus purified was distilled at 162–165°; it was then dried and fractionated taking the cut 164.8–164.9° at 759 mm. Analysis showed this to be 99.25% pure. The dimethyl amides of butyric, heptoic and caprylic acids were made similarly. With the higher acids a new difficulty was encountered; the potassium salt of the acid is soluble in the dimethyl amide. In such cases the reaction product was taken up in a large volume of benzene and this solution shaken with potassium hydroxide solution, dried and distilled. Franchimont and Klobbie prepared heptoic dimethyl amide by this method.

Other dimethyl amides were obtained in good yields by adding the acid chloride dropwise during three hours to a

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[1] From a part of the Ph.D. dissertation of John R. Ruhoff, 1932.

[2] Kewaunee Manufacturing Company Fellow in Chemistry, 1929–33.

[3] (a) A. P. N. Franchimont, *Rec. trav. chim.*, **2**, 332 (1883); (b) A. P. N. Franchimont and E. A. Klobbie, *ibid.*, **6**, 247 (1887); (c) A. P. N. Franchimont and H. A. Rouffaer, *ibid.*, **13**, 336 (1894); (d) A. Verley, *Bull. soc. chim.*, [3] **9**, 690 (1893); (f) *J. Russ. Phys.-Chem. Soc.*, **29**, 227 (1897); (e) M. Tiffeneau and K. Fuhrer, *Bull. soc. chim.*, [4] **15**, 169–170 (1914).

[4] Mitchell and Reid, THIS JOURNAL, **53**, 1879 (1931).

[5] Van der Zande, *Rec. trav. chim.*, **8**, 233 (1889).

[6] Peters and Baker, *Ind. Eng. Chem.*, **18**, 69 (1926).