[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE OHIO STATE UNIVERSITY]

The Synthesis of Hydroaromatic Compounds Containing Angular Groups. I. Hydrophenanthrene Series[1]

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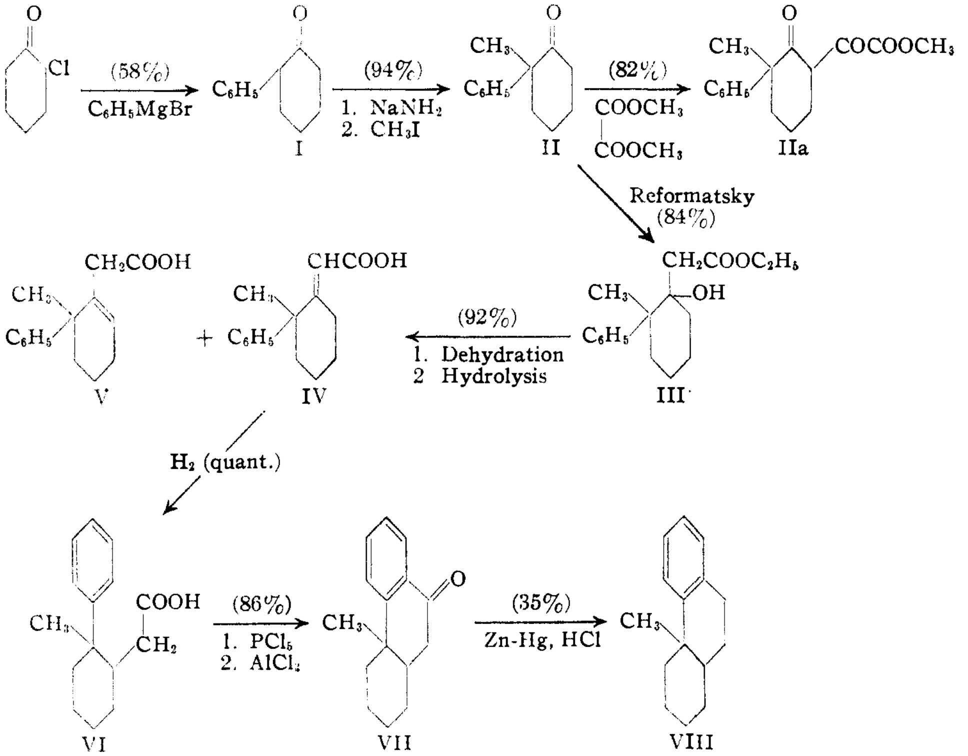
For some time we have been interested in the synthesis of hydroaromatic compounds containing angular groups. More specifically, we desire tetracyclic compounds having the steroid nucleus, or the closely related hydrochrysene structure, in which the oxygen functions are not in the same relative positions as in oestrone or equilenin and the angular group is not necessarily methyl. Such compounds are wanted for physiological testing of various kinds. In order to test the synthetic schemes in mind we have carried out reactions with simpler molecules and in this paper we report the synthesis of 4a-methyl-9-keto-1,2,3,4,4a,9,10,10a-octahydrophenanthrene, VII. The reactions are outlined below.



The chlorocyclohexanone was prepared most easily by chlorination of cyclohexanone in water suspension.[3] The reaction with phenylmagnesium bromide gave pure 2-phenylcyclohexanone, I, in 58% yield. It is not known whether the phenyl group is joined to the carbon which originally formed the carbonyl group or to the carbon which had the chlorine. In this case it makes no difference in the structure of the final ketone but in other cases the structure would have to be determined.

The angular methyl group was introduced in the desired position by alkylation using sodium amide and methyl iodide. A high yield of 2-methyl-2-phenylcyclohexanone, II, was obtained. To prove the location of the methyl group a benzal derivative was formed. This proved unsuitable for characterization and in its place the crystalline glyoxalate, IIa, was prepared. Since this introduced a new asymmetric carbon a mixture of stereoisomers was formed. However, the formation of the glyoxalate derivative in high yield is proof that a methylene group was adjacent to the carbonyl.[4]

The Reformatsky reaction went vigorously but largely by enolization,[5] as almost 50% of unreacted ketone was recovered in each run. The yield of III on the basis of ketone consumed was

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(2) Anna Fuller Fund Fellow. Part of the material presented was taken from the Ph.D. Thesis of M.D.F., Ohio State University, August, 1943.

(3) Compare Bartlett and Rosenwald, THIS JOURNAL, **56**, 1990 (1934); Kötz and Grethe, *J. prakt. Chem.*, (2) **188**, 473 (1909).

(4) Kötz and Blendermann, *ibid.*, [2] **88**, 257 (1913); Cornubert, *et al.*, *Bull. soc. chim.*, [4] **49**, 1381 (1931); Copp and Simonsen, *J. Chem. Soc.*, 415 (1940).

(5) Newman, THIS JOURNAL, **64**, 2131 (1942).

high. The dehydration of the hydroxy ester, III, was accomplished in high yield by treating with thionyl chloride and pyridine. After hydrolysis a mixture of a solid and liquid unsaturated acid was obtained. The structure of the solid acid, IV, was established by ozonization, a 61% yield of the semicarbazide of II being isolated from the neutral products. On ozonization of the liquid acid, V, followed by alkaline hydrolysis and cleavage, a small amount of α-methyl-α-phenyladipic acid[6] was isolated. The structures indicated in the formulas for IV and V were further supported by the values for their iodine numbers. Acid IV had an iodine number of 0.4 and V had 59. The theoretical for an acid of this size is 110. It has been shown that α,β-unsaturated acids have very low iodine numbers and β,γ-unsaturated acids somewhat higher values.[7]

The solid isomer, IV, was easily reduced over Adams platinum catalyst in quantitative yield to a mixture of solid saturated isomers of formula VI. This mixture was not separated into pure isomers but was used directly for cyclization. The liquid unsaturated acid, V, resisted a few attempts at hydrogenation and was not further used. Cyclization of the isomers of formula VI by an internal Friedel–Crafts reaction gave in high yield a mixture of stereoisomeric ketones of formula VII. Fractional recrystallization of the semicarbazones followed by hydrolysis yielded a pure isomer of VII.

The Clemmensen reduction of VII (mixture of isomers) yielded VIII, the physical constants of which agreed with those previously reported for this compound.[8] On dehydrogenation over selenium pure phenanthrene was obtained in high yield.

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Experimental[9]

2-Chlorocyclohexanone.—In a three-liter three-necked flask fitted with a gas inlet tube, a sealed mechanical stirrer arranged to provide splashing, and a gas outlet tube connected to a mercury valve were placed 294 g. of cyclohexanone and 900 cc. of water. After sweeping out the reaction vessel with chlorine, the gas outlet tube was connected to the mercury valve, the flask was cooled in an ice-bath, and 215 g. of chlorine was bubbled in during rapid stirring as quickly as the gas was absorbed (about forty-five minutes). The heavier chlorocyclohexanone layer was separated and combined with three 150-cc. ether-extracts of the aqueous phase. After removal of the ether, the residue was vacuum distilled from a modified Claisen flask, the fraction boiling below 100° at 10 mm. being collected. The crude product was then carefully fractionated to yield 265 g. (66%) of 2-chlorocyclohexanone,[3] b. p. 90–91° at 14–15 mm. This product showed a long flat at 23.2° in a time–temperature cooling curve. In addition 40 g. of cyclohexanone was recovered.

2-Phenylcyclohexanone, I.—A solution of 280 g. of 2-chlorocyclohexanone in 750 cc. of dry ether was added with stirring to 750 cc. of 3.22 *M* phenylmagnesium bromide at a rate which caused gentle refluxing (one hour). The ether was distilled until the foaming viscous residue almost filled the flask. After addition of 700 cc. of dry benzene the mixture was refluxed for eight hours. The reaction mixture was then hydrolyzed in the cold with water and the pure ketone, I, was obtained after vacuum fractionation as a colorless solid, b. p. 136–137° at 5–6 mm., f. p. 53–55°, in 58% yield. This procedure was worked out by Dr. John A. Cathcart, a previous Anna Fuller Fund Fellow.

2-Methyl-2-phenylcyclohexanone, II.—A suspension of 50 g. of sodamide in 700 cc. of dry ether was heated to reflux. Then a solution of 200 g. of 2-phenylcyclohexanone in 350 cc. of dry ether and 150 cc. of dry benzene (S-free) was added dropwise during one hour. After refluxing for another hour until the evolution of ammonia had ceased, the mixture was cooled and treated with a solution of 250 g. of methyl iodide in 350 cc. of dry ether. On warming an exothermic reaction occurred. After refluxing for two hours (one hour spontaneously) the mixture was treated with water and the solvents removed from the organic layer. On careful fractionation 198 g. (94%) of II, b. p. 95.5–96.5 at 1 mm., n^{20}_D 1.5357, was obtained.

Anal. Calcd. for $C_{13}H_{16}O$: C, 82.9; H, 8.6. Found[a]: C, 82.8, 82.7; H, 8.6, 8.5.

The semicarbazone of II was prepared in almost quantitative yield and melted at 207–208° with decomposition.

Anal. Calcd. for $C_{14}H_{19}ON_3$: C, 68.5; H, 7.8; N, 17.1. Found[a]: C, 68.6, 68.5; H, 8.0, 8.0; N, 17.2, 17.1.

The methyl glyoxalate derivative, IIa, prepared in 82% yield as described by Bachmann[10] for a similar case, melted from 99 to 103°. Presumably it was a mixture of the possible stereoisomers. A pure derivative, m. p. 117.4–117.9°, was obtained by fractional recrystallization from aqueous methanol.

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.1; H, 6.6. Found[a]: for mixture, m. p. 99–103°, C, 70.0, 70.0; H, 6.8, 6.7 For pure isomer m. p. 117°, C, 69.7, 69.8; H, 6.8, 6.7.

Ethyl 2-Methyl-2-phenylcyclohexan-1-ol-1-acetate, III.—The Reformatsky reaction between II (195 g.) and ethyl bromoacetate (208 g.) was carried out as usual[5] and was very vigorous. After working up in the usual manner, except that dehydrating conditions were avoided, the hydroxy ester was obtained by fractionation under reduced pressure in a modified Claisen flask. The ketone II was recovered in 48% yield and 116 g. (43% or 84% based on II consumed) of III was obtained as a viscous pale colored liquid, b. p. 135° at about 0.5 mm., n^{20}_D 1.5278.

Anal. Calcd. for $C_{17}H_{24}O_3$: C, 73.9; H, 8.8. Found[a]: C, 74.1, 74.1; H, 8.8, 8.6.

On saponification of this ester an acid, m. p. 144.4–144.8°, was obtained after several crystallizations from benzene.

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.5; H, 8.1. Found[a]: C, 72.4, 72.3; H, 7.9, 8.0.

2-Methyl-2-phenylcyclohexylideneacetic Acid, IV, and 2-Methyl-2-phenylcyclohexenylacetic Acid, V.—In a typical experiment, 166 g. of the hydroxyester III was dehydrated in 92% yield using thionyl chloride and pyridine[11] to give a mixture of unsaturated esters which was separated into 63 g. of a lower boiling (127°) and 38 g. of a higher boiling (127–132° at 0.5 to 1 mm.) fraction having n^{20}_D 1.5343 and 1.5360, respectively.

Anal. Calcd. for $C_{17}H_{22}O_2$: C, 79.0; H 8.6. Found[a]: for lower fraction, C, 79.5; H, 8.6; for higher fraction, C, 79.2, 79.2; H, 8.4, 8.5.

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[6] Following paper, Newman and Closson, THIS JOURNAL, **66**, 1553 (1944).

[7] Bull, "Biochemistry of the Lipids," J. Wiley and Sons, Inc., New York, N. Y., 1937, p. 86.

[8] Perlman, Davidson and Bogert, *J. Org. Chem.*, **1**, 288 (1936), give b. p. 145–147 at 10 mm., n^{25}_D 1.5508; Kon, *J. Chem. Soc.*, 1081 (1933), gives b. p. 157 at 16 mm., $n^{18.3}_D$ 1.5543.

[9] All melting points corrected. All careful fractionations under vacuum were carried out in modified Vigreux heated columns fitted with total reflux partial take-off heads. Analyses marked[a] by J. E. Varner, *b* by J. A. Curtiss, *c* by F. J. Baur.

[10] Bachmann, Cole and Wilds, THIS JOURNAL, **62**, 824 (1940).

[11] "Organic Reactions," Wiley and Sons, Inc., New York, N. Y., 1942, p. 12.

On hydrolysis of these esters approximately the same mixture of solid, IV, and liquid, V, unsaturated acids was obtained from the lower and higher boiling fractions, hence in further work no effort was made to make this separation. On standing the acid fractions partly crystallized. The mixture was triturated with low boiling petroleum ether (Skellysolve F) and the solid acid thus obtained was recrystallized to a melting point of 119–121°. The remaining acid was distilled and obtained as a viscous liquid, b. p. 172° at 2 mm.

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.2; H, 7.9. Found[a]: for solid isomer, C, 78.6, 78.4; H, 7.8, 7.7. For liquid acid, C, 78.5, 78.6; H, 7.7, 7.8. Iodine number: Calcd., 110. Found[c]: for solid isomer, 0.4; for liquid isomer, 59.0.

Ozonization of IV and V.—A solution of 0.45 g. of pure IV in 35 cc. of methanol was ozonized[12] for one hour. The solvent was removed under diminished pressure and the residue hydrolyzed with water. The neutral product remaining after an alkaline extraction was treated with semicarbazide and yielded 61% of the semicarbazone of II, m. p. 205–207°, mixed melting point with authentic sample not depressed. The solution containing the salts of the acid material gave a precipitate with calcium chloride which was apparently calcium oxalate, but this was not definitely established.

A solution of 8.6 g. of the liquid unsaturated acid, V, in 80 cc. of ethyl acetate was ozonized for seven hours.[12] This isomer absorbed ozone incompletely and at a slow rate. The ozonide was cleaved by hydrogenation over a palladium–calcium carbonate catalyst[12] and the cleaved product returned to the ozonizer to oxidize any aldehyde formed. The solution which now contained some peracid was again reduced over the same catalyst and the reaction products separated into acid and neutral fractions after boiling for one hour with 20% potassium hydroxide solution. No pure ketone or ketonic derivative was isolated from the neutral fraction. From the acidic fraction there was isolated a small amount of an acid, m. p. 114.4–114.9°, which gave analyses consistent with its formulation as α-methyl-α-phenyladipic acid. There was no depression of the melting point when mixed with an authentic sample of this acid.[6]

2-Methyl-2-phenylcyclohexylacetic Acid, VI.—The crystalline acid, IV, was reduced quantitatively in acetic acid over Adams platinic oxide catalyst. After removal of the catalyst and solvent the vacuum distilled acid crystallized, this crude mixture of stereoisomers melting at 85–98°. Recrystallization from a variety of solvents invariably yielded an acid mixture which melted over the range 101–114° and whose melting range was not raised or narrowed by recrystallization. A small amount of a pure isomer was finally obtained by partial neutralization of an aqueous sodium salt solution. Recrystallization of the acid fractions first precipitated by the addition of insufficient quantities of dilute hydrochloric acid yielded an acid which melted sharply at 131°. This treatment was not repeated on a large scale and the next step was carried out with the mixture of acids of formula VI.

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.5; H, 8.7. Found[a]: C, 77.7, 77.5; H, 8.7, 8.5. Acid, m. p. 131°, C, 77.6, 77.6; H, 8.7, 8.6.

4a-Methyl-9-keto-1,2,3,4,4a,9,10,10a-octahydrophenanthrene, VII.—The cyclization of the acid chloride of VI went smoothly in benzene solution. The ketone, VII, was obtained in 86% yield as a colorless liquid, b. p. 125–138° at 0.5 to 1 mm., $n^{20}D$ 1.5673. An attempt to separate an isomer by careful fractionation under reduced pressure was made but without success. Accordingly a quantity of the mixture of isomeric ketones was converted (almost quantitatively) into the semicarbazones. After systematic fractional crystallization, about one-third was obtained as white crystals, m. p. 204–206° with dec. when heated at the rate of two degrees per minute. The ketone formed by hydrolysis with dilute sulfuric acid formed a colorless liquid, b. p. 152–153° at 3–3.5 mm., $n^{20}D$ 1.5694, $n^{25}D$ 1.5672.

Anal. Calcd. for $C_{15}H_{18}O$: C, 84.1; H, 8.5. Found[b]: (for isomer mixture) C, 83.8, 83.7; H, 8.7, 8.5; (for pure isomer) C, 84.2, 84.3; H, 8.4, 8.5. Calcd. for $C_{16}H_{21}ON_3$: C, 70.8; H, 7.8; N, 15.5. Found[b]: (for isomer mixture) C, 70.3, 70.6; H, 7.9, 7.9; N, 15.8, 15.6; (for pure isomer) C, 71.0, 71.1; H, 8.0, 8.1; N, 15.7, 15.7.

4a-Methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene, VIII.—The crude ketone, VII, was reduced by Martin's modification of the Clemmensen method.[13] The crude reduction product was treated with Girard reagent P[14] to remove unreacted ketonic material and was then vacuum distilled to give in 35% yield a colorless liquid, b. p. 98–100° at 0.5–1 mm., $n^{20}D$ 1.5528, $n^{25}D$ 1.5508.[8]

Anal. Calcd. for $C_{15}H_{20}$: C, 89.9; H, 10.1. Found[b]: C, 90.3; H, 9.8.

Selenium Dehydrogenation.—A mixture of 1.3 g. of VIII and 2.6 g. of powdered selenium was heated at 290–320° for fifteen hours. The mixture was then extracted with benzene, the benzene was removed, and the residue was crystallized from alcohol. One gram of crude phenanthrene, m. p. 91–94°, was isolated. On recrystallization pure phenanthrene, m. p. and mixed m. p. with an authentic sample, 98.8–99.5°, was obtained.

Summary

The steps in the synthesis of 4a-methyl-9-keto-1,2,3,4,4a,9,10,10a-octahydrophenanthrene, VII, are described. The angular group in this synthesis is introduced by the alkylation of 2-phenylcyclohexanone. A two-carbon acid chain is then introduced at the ketonic carbon by means of the Reformatsky reaction, followed by dehydration and reduction. Finally, an intramolecular ring closure by the Friedel–Crafts method yields the desired ketone.

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(12) Henne and Hill, THIS JOURNAL, **65**, 752 (1943); Henne and Perilstein, *ibid.*, **65**, 2183 (1943).

(13) Martin, *ibid.*, **58**, 1438 (1936).

(14) Girard and Sandulesco, *Helv. Chim. Acta*, **19**, 1095 (1936).