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

The Synthesis of Hydroaromatic Compounds Containing Angular Groups. II. Cyclopentanonaphthalene Series[1]

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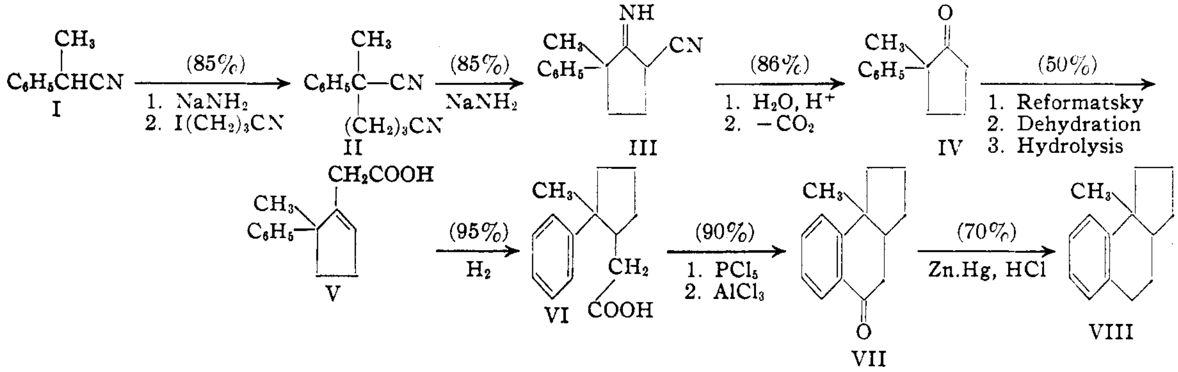
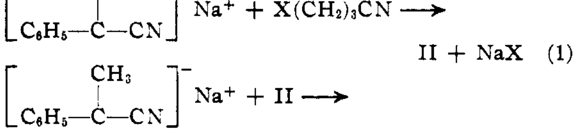
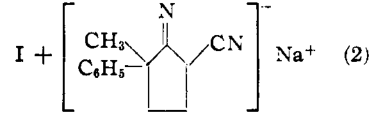
The present work was undertaken as a model for the synthesis of cyclopentanophenanthrene derivatives containing angular groups and having oxygenated functions at positions other than that occupied by the ketone group of oestrone. These compounds are desired for testing with regard to possible physiological activity. In this paper we report on the synthesis of 1-methyl-4-keto-1,2,3,4-tetrahydro-1,2-cyclopentanonaphthalene, VII, and the hydrocarbon, VIII, derived therefrom. The steps are outlined below.



The starting methylphenylacetonitrile, I, was prepared by the dehydration of hydratropaldehyde oxime. This method for preparing I was preferred to direct methylation of benzyl cyanide because a purer product is obtained. However, for groups other than methyl, direct alkylation would be simpler. The alkylation of I with γ-halobutyronitrile proved difficult to accomplish in good yield until carried out at −78° in toluene-ether. This is probably due to the fact that several competitive reactions may occur, as follows



$$\left[C_6H_5-\overset{CH_3}{\overset{|}{C}}-CN\right]^- Na^+ + X(CH_2)_3CN \longrightarrow II + NaX \quad (1)$$



any anion $A^-Na^+ + X(CH_2)_3CN \longrightarrow$ $AH + NaX + {:}CN$ (3)

At room temperature or higher, reactions 2 and 3 occur so readily that no appreciable amounts of II were obtained. At −78°, however, reactions 2 and 3 do not take place rapidly but reaction (1) still proceeds well enough so that an 85% yield of pure II was obtained.

It is possible to carry out both the alkylation of I to II and the cyclization of II to III in the same reaction mixture but better yields were obtained by carrying out the reactions separately. The dinitrile II was efficiently cyclized to III by sodium amide in refluxing benzene. A summary of the experiments done is contained in the Experimental Part.

On acid hydrolysis, III was converted into IV in high yield. The Reformatsky reaction proceeded vigorously but largely by enolization.[3] The unsaturated acid fraction obtained after dehydration and hydrolysis was separated into a mixture of about equal parts of a solid acid, m. p. 71–72°, and a non-crystalline portion. An attempt to prove the structure of the solid isomer by ozonization failed to give a pure compound. The solid unsaturated acid, V, was reduced to give a mixture of crystalline stereoisomeric saturated acids,[4] VI, which was not separated but cyclized directly by an internal Friedel–Crafts reaction into a mixture of stereoisomeric ketones, VII. A pure isomer of VII was obtained by fractional recrystallization of the semicarbazones followed by hydrolysis. Its properties were practically the same as those of the mixture, as was also the case with the pure hydrocarbon, VIII, produced on Clemmensen reduction. These properties also agreed with those recorded by Kon who previously prepared a mixture of the isomers of this hydrocarbon.[5]

The authors would like to take this opportunity to thank the Trustees of the Anna Fuller Fund for a grant in support of this work.

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(1) Presented before the Organic Division at the American Chemical Society meeting in Cleveland, April 3, 1944.

(2) Anna Fuller Fund Fellow. The material herein presented is contained in the Ph.D. Thesis of R. D. C., Ohio State University, June, 1944.

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

(4) Ghosh, *Chem. Zentr.*, **109**, I, 4319 (1938) reports one form of VI, m. p. 85°.

(5) Kon, *J. Chem. Soc.*, 1081–1087 (1933).

Experimental[6]

Hydratropaldehyde.—To a stirred solution of 274 g. of sodium hydroxide in 770 cc. of water was added 708 g. of ethyl β-methyl-β-phenylglycidate.[7] After stirring for eight hours at 45–50°, the solution was acidified to congo red. The glycidic acid was extracted with benzene and subjected to superheated steam distillation at 180°, during which decarboxylation occurred and the aldehyde distilled during about five hours. The pure aldehyde, 268 g. (58%), boiled at 101–102° at 21–22 mm.

Hydratropaldoxime.—Upon addition of 80 cc. of pyridine to a mixture of 20 g. of hydratropaldehyde, 40 cc. of water, and 25 g. of hydroxylamine hydrochloride considerable heat was evolved. After refluxing for five hours, the mixture was poured into dilute acetic acid and the oxime was extracted with benzene. Vacuum distillation gave 21 g. (94%) of oxime, b. p. 114–115° at 2–3 mm. Larger runs were made with similar results.

Hydratroponitrile, I.—A solution of 60 g. of oxime in 200 cc. of acetic anhydride was placed on a three-foot packed column (single turn Pyrex helices). The acetic acid was removed as formed during four to five hours. The excess acetic anhydride was removed under reduced pressure and 47.5 g. (89.5%) of nitrile, b. p. 107–110° at 11 mm., was obtained.

α-Methyl-α-phenyladiponitrile, II.—The sodium derivative of I was prepared under dry nitrogen by adding 16.3 g. of I to a suspension of 5.1 g. of sodium amide in 30 cc. of dry toluene and refluxing for twenty minutes. After cooling, 30 cc. of dry ether was added to dissolve the sodium derivative. The solution was then cooled to −78° with a dry-ice-bath and a solution of 23.8 g. of γ-iodobutyronitrile in 20 cc. of ether was added dropwise during one hour. After stirring at this temperature for two hours the reaction mixture was allowed to come to room temperature overnight and was then refluxed for ten minutes. Water was added and the dinitrile isolated and vacuum distilled to yield 21.5 g. (87.5%) of II, b. p. 150–160° at 1 mm.

Anal.[b] Calcd. for $C_{13}H_{14}N_2$: C, 78.8; H, 7.1; N, 14.2. Found: C, 78.3, 78.5; H, 7.1, 6.8; N, 14.4, 14.4.

Many experiments were carried out before this method of alkylation was tried. In all of these, the sodium derivative was prepared and the product isolated as above. The results are summarized in Table I.

TABLE I

ALKYLATION OF HYDRATROPONITRILE WITH γ-HALOBUTYRONITRILES

γ-Halonitrile	*T*, °C.	Time	% I	% II	% III	C_3H_5CN[a]
$Cl(CH_2)_3CN$	50	14 hr.	72	Trace	10	+
$Br(CH_2)_3CN$	80	40 min.	50	Trace	20	+
$I(CH_2)_3CN$	80	30 min.	50	Trace	30	+
$Br(CH_2)_3CN$	110	30 min.	30	Trace	—	+
$I(CH_2)_3CN$	−78	4 hr.	5	85	—	—

[a] The plus sign indicates that appreciable quantities of cyclopropyl cyanide were formed. However, the amounts formed were not accurately determined.

α-Methyl-α-phenyladipic Acid.—A solution of 2 g. of II in 30 cc. of acetic acid, 2 cc. of concentrated sulfuric acid, and 2.5 cc. of water was refluxed for forty-eight hours, 15 cc. of acetic acid being allowed to distill at the end. After dilution with water, the organic acid fraction was extracted with ether–benzene. The solvents were removed and 1.9 g. of crystalline acid was obtained by crystallizing from benzene–petroleum ether. This material had an unsharp melting range from 68 to 75° owing to solvation and to the presence of polymorphic forms. When these crystals were heated under vacuum to 78°, they fused and shortly resolidified. The new solid melted at 109–112° and on crystallization from benzene–petroleum ether gave crystals which again would fuse on heating *in vacuo* up to 78°. However, on recrystallization from aqueous acetic acid, stout colorless prisms, m. p. 113.7–114.6° cor., were obtained. A mixed melting point with a sample of α-methyl-α-phenyladipic acid obtained from the ozonization of 2-methyl-2-phenylcyclohexenylacetic acid[8] showed no depression.

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.1; H, 6.8; neut. equiv., 118. Found: C, 65.5, 65.5; H, 6.8, 6.7; neut. equiv., 117.

γ-Iodobutyronitrile.—To a solution of 160 g. of sodium iodide in 825 cc. of dry acetone was added 148 g. of γ-bromobutyronitrile. After standing for two hours at room temperature, most of the acetone was distilled during two hours. The product was taken into benzene, washed with sodium bisulfite, and vacuum distilled to yield 189 g. (96%) of γ-iodobutyronitrile, b. p. 73–74° at 0.5–1 mm.

3-Methyl-3-phenyl-2-iminocyclopentyl Cyanide, III.—To a suspension of 3.0 g. of sodium amide in 50 cc. of dry benzene under nitrogen was added 14.7 g. of II in 20 cc. of benzene. After refluxing for thirty minutes ammonia was no longer evolved. The mixture was cooled and treated with dilute acid. On removing part of the benzene and adding petroleum ether (90–97°) 12.5 g. (85%) of ketimine nitrile, III, m. p. 96–97°, crystallized.

Anal.[b] Calcd. for $C_{13}H_{14}N_2$: C, 78.8; H, 7.1; N, 14.2. Found: C, 78.5, 78.5; H, 6.9, 7.1; N, 14.3, 14.2.

The iminonitrile was further characterized by converting into the acetimino compound by means of acetyl chloride and pyridine in ether. It melted at 144.7–145.1° cor. after crystallization from benzene.

Anal.[b] Calcd. for $C_{15}H_{16}N_2O$: C, 75.0; H, 6.7; N, 11.7. Found: C, 74.5, 74.7; H, 6.6, 6.5; N, 11.4, 11.5.

2-Methyl-2-phenylcyclopentanone, IV.—A solution of 38 g. of III, 350 cc. of acetic acid, 20 cc. of water, and 20 cc. of concentrated sulfuric acid was refluxed for four hours and most of the acetic acid was distilled during two more hours. Following the addition of 400 cc. of water and extraction with benzene, 28.7 g. (86%) of ketone, IV, b. p. 90–98° at 1–2 mm., was obtained.

Anal.[b] Calcd. for $C_{12}H_{14}O$: C, 82.8; H, 8.1. Found: C, 82.8, 83.0; H, 8.3, 8.1.

The benzal derivative, m. p. 91–91.7°, and the semicarbazone, m. p. 191.0–191.4° cor., were formed in high yield for characterization.

Anal. Calcd. for $C_{13}H_{17}N_3O$: C, 67.5; H, 7.4; N, 18.2. Found[a]: C, 67.6, 67.6; H, 7.3, 7.4; N, 18.2, 18.2. Calcd. for $C_{19}H_{18}O$: C, 87.0; H, 6.9. Found[b]: C, 86.7, 86.9; H, 7.1, 6.9.

5-Methyl-5-phenyl-1-cyclopentene-1-acetic Acid, V.—After a typical Reformatsky reaction using 58 g. of IV, 65 g. of ethyl bromoacetate, and 200 cc. of benzene there was obtained 57 g. of an oil, b. p. 92–165° at 1 mm. To a solution of this and 30 cc. of pyridine in 150 cc. of dry ether was added 20 g. of pure thionyl chloride. After two hours at 0° and fifteen minutes at room temperature, the excess thionyl chloride was hydrolyzed and the organic material was distilled to give 51 g. of oil, b. p. 92–140° at 1 mm. After alkaline saponification there was isolated 25.5 g. (44%) of ketone, IV, and 20.8 g. (28%, or 50% allowing for recovered ketone) of unsaturated acid, V. From this acid mixture 10.8 g. of crystalline V, m. p. 69.5–72°, was isolated by crystallization from petroleum ether (90–97°). A sample recrystallized for analysis melted at 70.9–71.9° cor.

Anal.[a] Calcd. for $C_{14}H_{16}O_2$: C, 77.8; H, 7.4. Found: C, 77.5, 77.7; H, 7.3, 7.2.

When one gram of V was ozonized in methanol and treated with acetic acid and hydrogen peroxide, no semicarbazone was obtained from the neutral fraction, nor could any solid acid be isolated.

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[6] All analyses (micro) by J. A. Varner marked *a*, by J. A. Curtiss marked *b*.

[7] Obtained from Van Ameringen-Haebler Co., through the courtesy of Dr. E. Theimer.

[8] See preceding paper, Newman and Farbman, THIS JOURNAL, **66**, 1550 (1944).

The liquid unsaturated acid, V, was not further examined, except in so far as one unsuccessful attempt at catalytic hydrogenation.

2-Methyl-2-phenylcyclopentylacetic Acid, VI.—The solid isomer of V was easily reduced in 95% yield to VI by shaking with hydrogen over Adams platinic oxide catalyst in acetic acid. The product boiled from 140 to 143° at 1 mm. An attempt to separate a pure isomer by fractional crystallization of the amides failed. The highest melting amide fraction melted from 90 to 92°.

Anal.[b] Calcd. for $C_{14}H_{18}O_2$: C, 77.1; H, 8.3. Found: C, 76.6, 76.5; H, 8.5, 8.6. Calcd. for $C_{14}H_{19}ON$: C, 77.4; H, 8.8; N, 6.5. Found: C, 77.4, 77.2; H, 8.6, 8.4; N, 6.5, 6.6.

4-Keto-1-methyl-1,2-cyclopentano-1,2,3,4-tetrahydronaphthalene, VII.—The acid chloride of VI was cyclized by stirring with a slight excess of aluminum chloride in benzene solution at 50 to 60° for forty-five minutes. The ketone, VII, b. p. 109–111° at 1 mm., was obtained in 90% yield. A part of the ketone isomer mixture was converted (quantitatively) into semicarbazones. On fractional recrystallization, a pure semicarbazone, m. p. 244–247° (dec.), was obtained. This was hydrolyzed to give a pure isomer, VII, which differed little in index of refraction and boiling point from the mixture of isomeric ketones, $n^{20}\mathrm{D}$ (pure) 1.5650, (mixture) 1.5652. A 2,4-dinitrophenylhydrazone, m. p. 221.8–222.2° cor., of the pure ketone was prepared.

Anal.[b] Calcd. for $C_{15}H_{19}N_3O$: C, 70.0; H, 7.4; N, 16.3. Found: C, 70.2, 70.1; H, 7.1, 7.1; N, 16.4, 16.3. Calcd. for $C_{20}H_{20}N_4O_4$: C, 63.2; H, 5.3; N, 14.7. Found: C, 63.1, 63.1; H, 5.4, 5.4; N, 14.2. Calcd. for $C_{14}H_{16}O$: C, 84.0; H, 8.0. Found: for mixture of isomers, C, 83.6, 83.6; H, 7.9, 7.9. for pure isomer, C, 83.6, 83.5; H, 7.9, 7.9.

1-Methyl-1,2-cyclopentano-1,2,3,4-tetrahydronaphthalene, VIII.—A part of the pure ketone, VII (1.33 g.), was reduced by the modified Clemmensen method.[9] The pure hydrocarbon, VIII, was obtained in 70% yield as a colorless liquid, b. p. 128–132° at 11 mm., $n^{20}\mathrm{D}$ 1.5472 (Kon[5] gives b. p. 128 at 12 mm., $n^{17.8}\mathrm{D}$ 1.5479).

Anal.[b] Calcd. for $C_{14}H_{18}$: C, 90.3; H, 9.7. Found: C, 90.5, 90.3; H, 9.6, 9.7.

Summary

The synthesis of 4-keto-1-methyl-1,2-cyclopentano-1,2,3,4-tetrahydronaphthalene, VII, is described. Hydratroponitrile is alkylated with γ-iodobutyronitrile to yield the dinitrile of α-methyl-α-phenyladipic acid. Internal cyclization followed by hydrolysis and decarboxylation yields 2-methyl-2-phenylcyclopentanone. A two-carbon acid chain is introduced at the ketonic carbon by the usual procedure involving the Reformatsky reaction, dehydration, hydrolysis and reduction. Finally, the resulting acid is cyclized to the desired ketone by an intramolecular Friedel–Crafts reaction.

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

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[Contribution from the Chemical Laboratory of the University of California]

The Interpretation of the Effects of Salts on the Rates of Some Hydrolytic Reactions

By A. R. Olson and L. K. J. Tong

In aqueous solutions, acetal, $CH_3CH(OC_2H_5)_2$, is stable enough at ordinary temperatures so that the "spontaneous" rate of hydrolysis to alcohol and aldehyde can be neglected.[1]

In the presence of hydrogen ions, the hydrolysis proceeds smoothly according to the first order equation

$$d \ln (A)/dt = \text{constant}$$

The addition of neutral salts to such an acid solution of acetal produces a change in the rate. It is this change which Brønsted[2] calls a "Medium Effect," and which he in the same article divides into a "primary kinetic salt effect" and a "secondary salt effect." The secondary effect influences the rate by changing the concentration of the hydrogen ions, *i. e.*, if a weak acid were present its dissociation in general would be changed by the addition of "inert" salts.

The primary salt effect involves the "kinetic activity factor" $\gamma_A\gamma_B/\gamma_X$ in the equation

$$R = kC_AC_B\frac{\gamma_A\gamma_B}{\gamma_X} \qquad (1)$$

for a reaction between A and B, where γ_A and γ_B are the activity coefficients of A and B, respectively, and γ_X the activity coefficient of some evanescent reaction complex. Setting $-\log \gamma = 0.5z^2\sqrt{\mu} + \beta\,\mu$ where z is the charge on a particle and μ is the ionic strength, the velocity equation (1) becomes

$$R = kC_AC_Be^{\mu(\beta_A + \beta_{H^+} - \beta_{X^+})}$$

for the acetal reaction. "This corresponds to a linear salt effect in the dilute range. As the β factor for the hydrogen ion is unusually large (and, therefore, larger than β_x) and for a non-charged molecule usually positive, we have reason to expect a positive salt effect in a hydrogen ion catalysis as actually found for such reactions."

The salt effects are indeed large—so large that we were led to believe that even if the above ideas are correct, some factors must be missing in the above rate expression, a conclusion to which Riesch and Kilpatrick[3] also came. These investigators, studying the hydrolysis of acetal in hydrochloric acid solution at 0°, concluded that "equation (1) is only approximately in agreement with experiment even in dilute solution."

We have, therefore, measured the rates of hydrolysis of acetal in a variety of solutions as well as those of dimethyl acetal and dipropyl formal. The latter react much more slowly than does

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[1] J. H. Brønsted and W. F. K. Wynne-Jones, *Trans. Faraday Soc.*, **25**, 59 (1929).

[2] J. N. Brønsted, *ibid.*, **24**, 630 (1928).

[3] C. C. Riesch and M. Kilpatrick, *J. Phys. Chem.*, **39**, 561 (1935).