The analyses for studies 3, 4 and 6 were unsuccessful, but inasmuch as the pressures had been very carefully measured, it was felt that they could still contribute to the heat of dissociation value. The P_o values for these samples were computed by making use of an equilibrium constant which had been calculated from the equation

$$\log K = -3347/T + 10.931 \qquad (7)$$

which is an average equation based on studies 1, 2, 5, 7 and 8. Equilibrium constants from studies 3, 4 and 6 have not been used in the computation of precision measures.

Equations for studies 1, 2, 5, 7 and 8 have been used to calculate equilibrium constants at the temperatures 80, 100 and 120°. The mean for the five values at the respective temperatures along with their respective probable errors are: 28.6 ± 0.7, 92.0 ± 0.8 and 262 ± 0.7%. The relative probable errors associated with the means appear to be nearly independent of the magnitude of the equilibrium constant. This relative error is believed to be associated with the equilibrium constants calculated with equation (7). The mean value of ΔH computed from all the studies is 15,270 calories with 70 calories being the probable error of a single value.

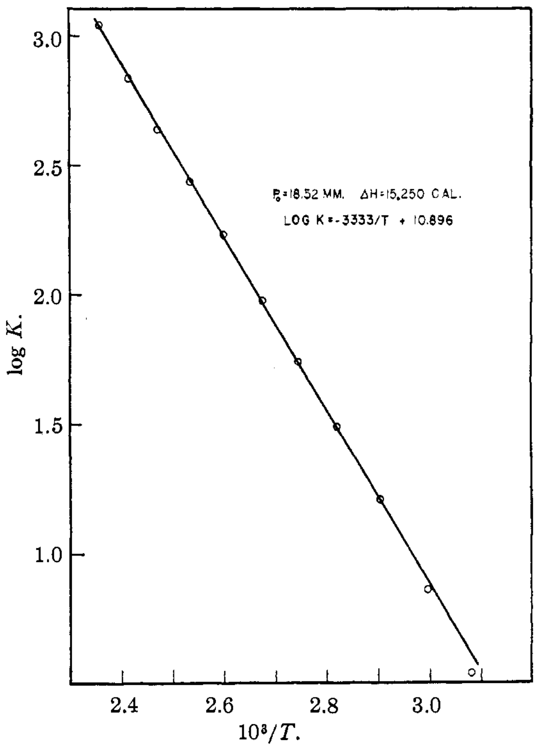

Fig. 1.—Summary of dissociation study—VIII.

Summary

The vapor phase dissociation of acetic acid has been studied over the pressure range (for dimer calculated to 0°) of 13 to 34 mm. and the temperature range of 50 to 150°. Data have been obtained from eight studies. The linearity of the middle portion of all the graphs suggests that dimer formation is the only phenomena occurring in this pressure range and that the value obtained for ΔH is the thermodynamic heat of dissociation. A heat of dissociation of 15,270 ± 100 cal. with a probability greater than 90% has been computed. An equation, $\log K = -3347/T + 10.931$, which is believed to express equilibrium constants to ±1.0% with a probability of 65% has been derived. The free energy of dissociation and the entropy of dissociation at 100° are computed to be 1,570 cal. and 36.7 cal./deg., respectively. At the triple point acetic acid exhibits a vapor pressure of 9.5 mm. Other values of the heat of dissociation of acetic acid which have been determined by vapor phase studies are 16.4,[8] 14.5,[9] 15.0,[10] 14.5[7] and 13.8[6] kcal.

WASHINGTON, D. C. RECEIVED JUNE 21, 1950

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF OBERLIN COLLEGE]

Synthesis of Some 2-Methoxy-8-keto-4a-methylperhydrophenanthrenes

BY W. B. RENFROW, ANTOINETTE RENFROW, ELLEN SHOUN AND C. A. SEARS

The stereoisomeric 2-methoxy-8-keto-4a-methylperhydrophenanthrenes (IV) are of interest as possible intermediates in the synthesis of steroids.[1]

Our synthesis involves a modification and extension of the method of Bardhan and Sengupta[2] and of Kon[3] for the synthesis of octahydrophenanthrenes.

We prepared 2-carboethoxy-4-methoxy-2-[2-(*o*-anisyl)-ethyl]-cyclohexanone (Ia) by alkylation of 2-carboethoxy-4-methoxycyclohexanone with 2-(*o*-anisyl)-ethyl bromide. Compounds like Ia do not undergo ketonic cleavage in satisfactory yield when heated with alkali,[2,3,4] but can be converted to ketones by indirect methods.[3,4] Methanolysis[5] of Ia to a substituted pimelic ester occurred readily and the pimelic ester was recyclized by removing methanol[6] to form the sodio derivative of 2-carbomethoxy - 4 - methoxy - 6 - [2-(*o*-anisyl) - ethyl]-cyclohexanone. The latter compound corresponds to a β-ketoester with one α-hydrogen atom and mild alkaline hydrolysis produced 4-methoxy-2-[2-(*o*-anisyl)-ethyl]-cyclohexanone (Ib) in satisfactory yield.

The ketone (Ib) was converted to 1-methyl-4-methoxy-2-[2-(*o*-anisyl)-ethyl]-cyclohexanol (II) with methylmagnesium iodide.

The method previously employed[2,3] for cyclizing 2-(2-phenylethyl)-cyclohexanols by distillation

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[1] Synthesis of a 2-hydroxy-8-keto-4a-methylperhydrophenanthrene by a different method has been reported by Cornforth and Robinson, *J. Chem. Soc.*, 676 (1946).

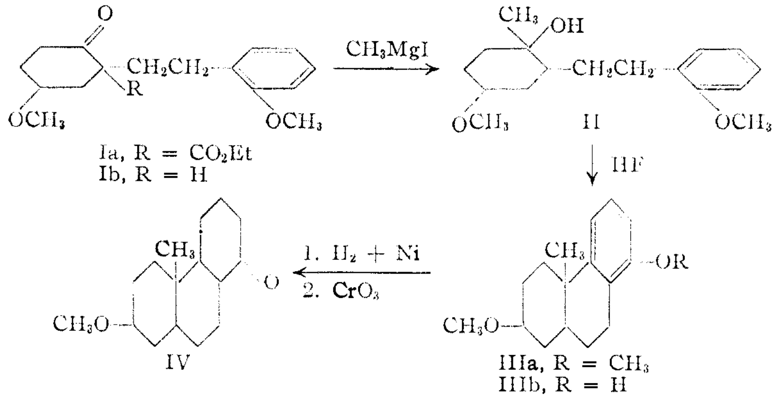
[2] Bardhan and Sengupta, *ibid.*, 2520 (1932).

[3] Kon, *ibid.*, 1081 (1933).

[4] Hibbit and Linstead, *ibid.*, 470 (1936).

[5] The alcoholysis of β-ketoesters has been studied by Kutz and Adkins, THIS JOURNAL, **52**, 4391 (1930).

[6] McElvain, *ibid.*, **51**, 3124 (1929).



from phosphorus pentoxide was found to cause elimination of the alicyclic methoxyl group when applied to II. We have cyclized II to 2,8-dimethoxy-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (IIIa) with anhydrous hydrogen fluoride.[7] The structure of IIIa was confirmed by dehydrogenation to 1-methoxyphenanthrene. This behavior on dehydrogenation is in agreement with the results of other workers.[1]

The aromatic methoxyl group in IIIa was cleaved by heating with potassium hydroxide in methanol[8] to produce a salt of IIIb. Two crystalline forms of IIIb and a glassy material which presumably consists of other stereoisomers have been isolated.

The aromatic ring in IIIb was hydrogenated with Raney nickel catalyst and a small amount of potassium hydroxide.[9] Oxidation of the hydrogenation product of IIIb with chromium trioxide gave IV. Two racemic forms of IV that are probably reasonably pure were obtained, as well as a mixture of isomers.

Experimental[10]

2-Carboethoxy-2-methoxy-2-[2-(*o*-anisyl)-ethyl]-cyclohexanone (Ia).—Potassium *t*-butoxide was prepared by stirring and refluxing 22.3 g. of potassium with 350 ml. of *t*-butanol until the metal had reacted. The reaction flask was flushed with dry nitrogen and 114 g. of 2-carboethoxy 4-methoxycyclohexanone[11] added. The solution was stirred for several minutes and 127 g. of 2-(*o*-anisyl)-ethyl bromide[12] added. The solution was stirred and refluxed for 12 hours. The reaction mixture was distilled until 250 ml. of distillate was collected. Water was added to dissolve precipitated potassium bromide. The layers were separated, the water layer extracted with benzene and the organic solution washed with water and dried with sodium sulfate. Solvent was removed and the residue distilled at 20 mm. with a thermometer in the liquid phase until the temperature of the boiling liquid reached 220°. This material (130 g., 68%) was sufficiently pure to be used in the next step. A sample was purified by distillation; b.p. 224-228° at 4 mm., $n^{25}\text{D}$ 1.5167, d^{25}_4 1.122.

Anal. Calcd. for $C_{19}H_{26}O_5$: C, 68.23; H, 7.84. Found: C, 68.09; H, 8.02.

4-Methoxy-2-[2-(*o*-anisyl)-ethyl]-cyclohexanone (Ib).—The crude ester (130 g.) from the experiment described above was added to a sodium methoxide solution prepared from 10.3 g. of sodium and 150 ml. of dry methanol. The solution was refluxed for four hours and distilled until 100 ml. of distillate was collected. Nitrogen was bubbled through the solution to prevent bumping during the distillation. Dioxane (75 ml., purified by refluxing with sodium) was added, a fractionating column attached and the mixture distilled until 115 ml. of distillate was collected and the temperature at the head of the fractionating column had reached 95°. The residue was poured while still hot into about 150 g. of ice and 350 ml. of water. Sodium hydroxide (25 g.) was added and the mixture stirred slowly overnight. Most of the material dissolved. The mixture was extracted with ether, the aqueous layer distilled for a short time to remove ether and then refluxed for four hours. The ketone separated and was extracted from the cooled mixture with four portions of carbon tetrachloride. The carbon tetrachloride solution was dried with sodium sulfate, the solvent removed and the product (66 g., 44% based on 2-carboethoxy-4-methoxycyclohexanone) boiling 205-215° at 10 mm. was collected. On fractional distillation, practically all of this material boiled at 204-207° at 8 mm., $n^{25}\text{D}$ 1.5262, d^{25}_4 1.084.

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.15; H, 8.67.

2,8-Dimethoxy-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (IIIa).—A Grignard reagent was prepared from 10 g. of magnesium, 230 ml. of ether and 57.2 g. of methyl iodide. The Grignard solution was chilled in an ice-bath and a solution of 83.6 g. of 4-methoxy-2-[2-(*o*-anisyl)-ethyl]-cyclohexanone (Ib) in 50 ml. of ether dropped in. The solution was refluxed for 30 minutes and allowed to stand overnight. The solution was poured onto 400 g. of ice and 11.6 ml. of sulfuric acid. The layers were separated and the water layer extracted with ether. The combined ether layers were washed with water, sodium bicarbonate solution and dried over sodium sulfate. The ether was distilled and the residue heated in a boiling water-bath at reduced pressure (20 mm.) for one hour to remove ether as completely as possible. The hot liquid was poured into a stainless steel beaker. The beaker was fitted with a top carrying an inlet tube for dry illuminating gas (to prevent condensation of moisture during the reaction) and a 2-cm. opening. The beaker was flushed with gas and cooled thoroughly in an ice-salt-bath. The material in the beaker was stirred as well as possible with a copper rod and 82 g. of anhydrous hydrogen fluoride added in small portions at first and in larger portions as the mixture became fluid. Rubber gloves were worn while handling the hydrogen fluoride, and the reaction was carried out in a good hood. After all the hydrogen fluoride was added and the mixture thoroughly stirred it was allowed to stand in the ice-bath for five minutes. If this mixture becomes warm the product is a tar. Cracked ice (about 250 g.) was added with stirring, followed by 350 ml. of water. The mixture was extracted with ether, the ether solution washed with water, sodium carbonate solution until alkaline, dried over potassium carbonate and distilled. The product (68.4 g., 83%) was collected at 195-205° at 10 mm. A fractionated sample boiled mostly 200-202° at 10 mm., $n^{25}\text{D}$ 1.5488, d^{25}_4 1.082.

Anal. Calcd. for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.32; H, 9.38.

Dehydrogenation of the Diether (IIIa).—The diether (1 g.) and 0.1 g. of a palladium-on-charcoal catalyst[13] were heated in a metal-bath at 345-355° for eight hours. The residue was extracted with ether, the ether filtered, the solvent removed and the residue (0.5 g.) distilled at 1 mm. The distillate (0.3 g.) crystallized on standing and was recrystallized from methanol to give 0.1 g. of white needles melting 98-100°; reported[14] for 1-methoxyphenanthrene, 105°. A picrate prepared from a portion of this material melted 149-151°; previously reported[14] for 1-methoxyphenanthrene picrate, 154°. Another portion (0.05 g.) of the needles melting 98-100° was heated at 185-195° for

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(7) Calcott, Tinker and Weinmayr, THIS JOURNAL, **61**, 1010 (1939).

(8) Heer, Billeter and Miescher, *Helv. Chim. Acta*, **28**, 1342 (1945).

(9) Ungnade and McLaren, THIS JOURNAL, **66**, 118 (1944), found that addition of alkali favored hydrogenation of certain alkyl phenols. Omission of the alkali in one of our experiments led to considerable hydrogenolysis.

(10) Melting and boiling temperatures were determined with partial immersion thermometers.

(11) Cook and Lawrence, *J. Chem. Soc.*, 58 (1938).

(12) Hewett, *ibid.*, 50 (1936); Sugasawa, *Ber.*, **74B**, 459 (1941).

(13) Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1941, p. 459.

(14) Fieser, THIS JOURNAL, **51**, 2468 (1929).

three hours with 0.28 g. of pyridine hydrochloride, water added, the mixture extracted with ether and the ether extracted with sodium hydroxide solution. Acidification of the sodium hydroxide solution gave a crystalline precipitate melting at 155°. The melting point was not changed by crystallization from benzene-ligroin; previously reported[14] for 1-phenanthrol, 157°.

2-Methoxy-4a-methyl-1,2,3,4,4a,9,10,10a-octahydro-8-phenanthrol (IIIb).—The diether (IIIa, 15 g.) was heated to 200-225° and shaken in the copper liner of a hydrogenation apparatus with 100 ml. of methanol and 30 g. of potassium hydroxide for five hours. The reaction mixture was diluted with 200 ml. of water and extracted with ligroin to remove turbidity. The alkaline solution was acidified with hydrochloric acid and extracted three times with ether. The ether solution was dried and distilled to yield 12.0 g. (85%) of very viscous liquid boiling 195-210° at 6 mm. The viscous liquid was dissolved in about twice its volume of ethanol and allowed to stand in a refrigerator, whereupon crystals formed. Repeated crystallization from ethanol produced two crystalline solids. The least soluble in ethanol crystallized as small tetrahedra melting 210-211°, and amounted to about 3.5% of the phenolic material. The other solid crystallized in large, clear prisms melting 169-170°, and amounted to about 25% of the phenolic material. The remainder of the phenol was recovered as a viscous oil from the mother liquors and distilled.

Anal. Calcd. for $C_{16}H_{22}O_2$: C, 78.02; H, 9.01. Found for phenol melting 210-211°: C, 78.05; H, 9.02. Found for phenol melting 169-170°: C, 77.99; H, 9.06. Found for non-crystalline phenol fraction: C, 78.34; H, 9.12.

2-Methoxy-8-keto-4a-methylperhydrophenanthrene (IV).—The procedure for converting phenols to ketones is illustrated by an experiment utilizing a mixture of all the isomeric phenols formed by cleavage of the diether (IIIa). The phenolic material (12 g.) was placed in the copper liner of a hydrogenation apparatus with 50 ml. of ethanol, five drops of 30% potassium hydroxide solution and about 1 g. of Raney nickel catalyst[15] and hydrogenated at a temperature of 150-160° and a hydrogen pressure of about 2000 p.s.i. for six hours. The catalyst was filtered off and the solution heated in an oil-bath at 125° to remove solvent. The residue was dissolved in benzene and extracted repeatedly with 10% sodium hydroxide solution to remove a small amount of unhydrogenated phenol. The benzene solution was washed with water, dried over potassium carbonate, the solvent removed and the residue heated in an oil-bath at 125° at reduced pressure to insure complete removal of the ethanol used as a solvent for hydrogenation. The remaining thick oil was taken up in 25 ml. of benzene and treated with a solution of 3.3 g. of chromium trioxide in 30 ml. of 50% aqueous acetic acid. The mixture was agitated until the heat of reaction was dissipated and then heated to 75°. The mixture was cooled, a solution of 2.6 ml. of sulfuric acid in 10 ml. of water was added and the temperature again raised to 75°. The layers were separated, the aqueous layer extracted with benzene and the benzene solution washed with water, sodium carbonate solution and dried over potassium carbonate. The solvent was removed and the residue refluxed one hour with 10 g. of Girard T reagent, 60 ml. of absolute ethanol and 8 ml. of acetic acid. The solution was poured onto 6.3 g. of sodium carbonate in 300 ml. of ice and water. Considerable tarry material separated. A filter aid was added, the solution filtered and extracted with ether. The water solution was treated with 25 ml. of concd. hydrochloric acid and allowed to stand overnight. The solution was extracted with ether, the ether layer washed with sodium carbonate solution and dried over potassium carbonate. Distillation gave 5.0 g. (41%) of an oil boiling 185-195° at 6 mm.

The ketone prepared by the above method from the isomer of IIIb melting 168-170° had the following properties: b.p. 203-204° at 9 mm., $n^{25}\text{D}$ 1.5291, d^{25}_4 1.077. A semicarbazone crystallized from dioxane melted 253-254° dec.

Anal. Calcd. for $C_{16}H_{26}O_2$: C, 76.76; H, 10.46. Found: C, 77.02; H, 10.15. Calcd. for $C_{17}H_{29}O_2N_3$: C, 66.43; H, 9.50. Found: C, 66.42; H, 9.25.

The ketone prepared from the non-crystalline phenol fraction was converted to a semicarbazone and crystallized from ethanol. About 30% of the material was obtained as a solid m.p. 235° dec. The mother liquors gave a gummy material that was presumably a mixture of semicarbazones of other isomers. A sample of the semicarbazone melting at 235° (3.7 g.) was converted back to the ketone with pyruvic acid[16]; b.p. 186-187° at 6 mm., $n^{25}\text{D}$ 1.5194, d^{25}_4 1.062.

Anal. Calcd. same as above. Found for ketone: C, 76.83; H, 10.19. Found for semicarbazone: C, 66.59; H, 9.26.

We have not accumulated enough of the phenol fraction melting 210-211° to make conversion to the ketone worthwhile.

Summary

2,8-Dimethoxy-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene can be prepared by cyclization of 1-methyl-4-methoxy-2-[2-(*o*-anisyl)-ethyl]-cyclohexanol with cold anhydrous hydrogen fluoride. The diether can be converted to 2-methoxy-8-keto-4a-methylperhydrophenanthrenes by standard methods.

OBERLIN, OHIO RECEIVED JULY 10, 1950

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[15] Pavlic and Adkins, THIS JOURNAL, 68, 1471 (1946).

[16] Hershberg, *J. Org. Chem.*, 13, 542 (1948).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MARYLAND]

Isocyanates of 9-Methyl- and 9,10-Dimethyl-1,2-benzanthracene

BY W. MAYO SMITH, JR.,[1] ERNEST F. PRATT AND HUGH J. CREECH

The results of immunological studies on hydrocarbon–protein conjugates, recently described,[2] indicated the desirability of testing certain additional coupling products of proteins and isocyanates of carcinogenic hydrocarbons.[3] The syntheses of 9-methyl- and 9,10-dimethyl-1,2-benzanthryl-3-isocyanates (IX and IXA) are described in this paper. Conjugates prepared from these isocyanates will be examined serologically; their potentialities for eliciting antisera capable of preventing hydrocarbon carcinogenesis also will be investigated.

The anthrone (IV) was the key intermediate from which both isocyanates were prepared. It was synthesized by a five-step process. The first step was the condensation of α-methoxynaphthalene with phthalic anhydride to give I by the method of Fieser and Dietz.[4] The lactone (II) was prepared by the action of methylmagnesium bromide on I and was converted to III by alkaline hydrolysis followed by reduction with zinc and

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[1] From a thesis submitted to the Faculty of the Graduate School of the University of Maryland in partial fulfillment of the requirements for the Ph.D. Degree.

[2] Creech, Oginsky and Cheerer, *Cancer Research*, 7, 290 (1947); Creech, Oginsky and Allen, *ibid.*, 7, 297 (1947); and Creech, Oginsky and Tryon, *ibid.*, 7, 301 (1947).

[3] Creech and Jones, THIS JOURNAL, 63, 1661, 1670 (1941).

[4] Fieser and Dietz, *ibid.*, 51, 3141 (1929).