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).

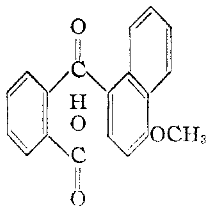
[3] Creech and Jones, THIS JOURNAL, **63**, 1661, 1670 (1941).

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

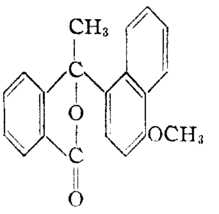
sodium hydroxide.[5] Cyclization to IV was readily accomplished with hydrofluoric acid.

Reduction of IV by the Meerwein–Ponndorf–Verley method gave the methylmethoxyanthrol (V) while reaction of IV with methylmagnesium bromide produced the corresponding dimethylmethoxyanthrol (VA). Each of these was converted to the desired isocyanate (IX and IXA) by dehydration (to VI and VIA), cleavage of the methoxyl group by hydrobromic acid, conversion of the resulting hydroxyl group to the amino group by the Bucherer reaction and treatment of the amine with phosgene. The 9-phenyl-10-methyl- and 9-ethyl-10-methylmethoxybenzanthracenes (XI and XII) were also prepared by condensation of the anthrone (IV) with the corresponding Grignard reagent and dehydration of the resulting anthrols.

Conditions were found under which yields of 68 to 98% were obtained in each step of these syntheses.



I



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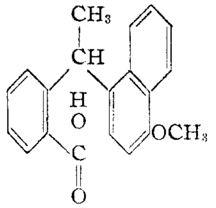
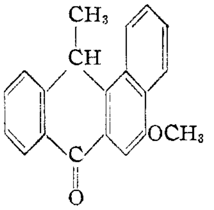
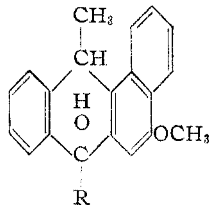


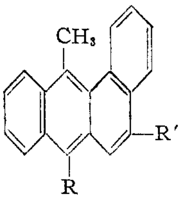
III



IV



V, R = H VA, R = CH_3



VI, R = H, R' = OCH_3
VIA, R = CH_3, R' = OCH_3
VII, R = H, R' = OH
VIIA, R = CH_3, R' = OH
VIII, R = H, R' = NH_2
VIIIA, R = CH_3, R' = NH_2
IX, R = H, R' = NCO
IXA, R = CH_3, R' = NCO
X, R = H, R' = $NHCOOC_2H_5$
XA, R = CH_3, R' = $NHCOOC_2H_5$
XI, R = C_6H_5, R' = OCH_3
XII, R = C_2H_5, R' = OCH_3

Experimental[6]

Lactone of 2-[α-Hydroxy-α-1'-(4'-methoxynaphthyl)-ethyl]-benzoic Acid (II).—The 2-(4'-methoxynaphthoyl-1')-benzoic acid (I) was prepared by the method of Fieser and Dietz.[4] By adding the aluminum chloride in small portions so that the temperature could be carefully controlled at 15 to 20° the amount of darkening was decreased and it was unnecessary to use decolorizing carbon. The pure acid was obtained by dispersing the sodium salt in cold water and acidifying with dilute sulfuric acid. A 95% yield of white, flocculent powder which melted at 196.5–197.0° was obtained. Analytical results have not been reported previously.

Anal. Calcd. for $C_{19}H_{14}O_4$: C, 74.49; H, 4.60. Found: C, 74.55; H, 4.58.

A solution of 5 moles of methylmagnesium bromide in 4 l. of ether was introduced below the surface of a well-stirred suspension of 519 g. (1.66 moles) of the acid (I) in 5 liters of toluene.[5] The muddy yellow suspension was refluxed for four hours and stirred overnight without heating; some material remained undissolved. Ice and hydrochloric acid were added, the layers were separated and the aqueous layer was repeatedly extracted with 2:1 benzene–ether. The combined non-aqueous layers were washed well with sodium carbonate solution, then with sodium chloride solution and dried over magnesium sulfate. Most of the solvents were removed under reduced pressure and one-fourth volume of absolute ethanol was added to the resulting red sirup. Petroleum ether (30–60°) was then added with swirling until a faint turbidity appeared. Upon cooling, 286 g. (57%) of light yellow product was obtained; two liquid phases were present when crystallization occurred. Evaporation of the solvent from the filtrate and molecular distillation of the residue gave an additional 57 g. (total yield 70%) of crystalline lactone; m.p. 139.8–140.5°.

Anal. Calcd. for $C_{20}H_{16}O_3$: C, 78.93; H, 5.30. Found: C, 78.82; H, 5.57.

2-[α-1'-(4'-Methoxynaphthyl)-ethyl]-benzoic Acid (III).—A solution of 364 g. of the lactone (II) in 8500 ml. of 95% ethanol and 850 ml. of 55% aqueous sodium hydroxide was refluxed for 24 hours.[5] Approximately 3 l. of the solvent was distilled and replaced by water; distillation was then continued until violent bumping occurred. Zinc dust (850 g.) activated with copper sulfate, 55% aqueous sodium hydroxide (1700 ml.) and water (4,000 ml.) were added and the mixture was refluxed 24 hours. The precipitate contained all the salt of the acid for acidification of the filtrate gave no additional solid. Extraction of the precipitate with hot water was carried out until acidification of a portion of the filtrate gave no more solid. The entire filtrate was acidified with dilute sulfuric acid and the product (III) was collected and washed free of sulfate ion with hot water. The microscopic needles, dried in a vacuum oven first at 45° and finally at 105°, weighed 358 g. (98%) and melted at 197.3–198.1°.

Anal. Calcd. for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92. Found: C, 78.38; H, 5.98.

3-Methoxy-9-methyl-1,2-benz-10-anthrone (IV).—Cyclization proceeded smoothly when a mixture of 25 g. of the acid (III) and 250 g. of anhydrous hydrofluoric acid in a copper vessel was swirled occasionally for ten minutes[7]; volatilization of the hydrogen fluoride controlled the temperature. The dark red solution was slowly added with vigorous stirring to about 2 l. of finely chopped ice. The anthrone, which separated as a brownish sand, was washed free of acid with ice water and, since attempts at recrystallization were unsuccessful, it was dried under reduced pressure and used without further purification. The crude product weighed 23.0 g. (98%).

3-Methoxy-9,10-dihydro-9-methyl-10-hydroxy-1,2-benzanthracene (V).—A solution of 29.4 g. of the crude anthrone (IV) in 250 ml. of anhydrous isopropyl alcohol was stirred vigorously while 62.4 g. of aluminum isopropoxide was added. The mixture was heated under reflux for seven hours and the volatile constituents were slowly distilled. Additional isopropyl alcohol was added, refluxing was continued for seven hours more, and the volatile material was removed as before. Three hundred ml. of 3:1 water–hydrochloric acid was added and the mixture extracted with benzene. The extract was washed well with water, dried over magnesium sulfate and concentrated by distillation. An 87% yield (25.8 g.) of crude product which resisted attempts at crystallization was obtained.

3-Methoxy-9-methyl-1,2-benzanthracene (VI).—The crude anthrol readily underwent dehydration when heated to 200° on the hot-plate, but the following method proved

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[5] This procedure is based on one used for a related compound by Newman, This Journal, **60**, 1368 (1938). See also Newman and Gaertner, *ibid.*, **72**, 264 (1950).

[6] All melting points are corrected. Microanalyses by Dr. Eleanor Werble.

[7] Fieser and Hershberg, This Journal, **61**, 1272 (1939).

to be superior. Most of the volatile constituents were removed from the reaction mixture from the Meerwein–Ponndorf–Verley reduction as described just above and 200 ml. of xylene was added. Upon further heating dehydration occurred and the water distilled with the xylene. The product was purified by converting it to the picrate and applying the chromatographic adsorption method.[8] A 1:1 mixture of alumina and supercel was the adsorbent. The benzene solution of the free benzanthracene (VI) which passed through the adsorption column showed intense blue fluorescence under ultraviolet light. Benzene solutions of the related compounds VIA, XI and XII also showed this fluorescence. Upon concentrating and cooling this solution 18.9 g. (78%) of pale yellow plates which melted at 123.9–124.3° was obtained. The over-all yield calculated from the methoxy acid (III) was 67%.

Anal. Calcd. for $C_{20}H_{16}O$: C, 88.20; H, 5.92; CH_3O–, 11.39. Found: C, 88.14; H, 6.07; CH_3O–, 11.36.

3-Amino-9-methyl-1,2-benzanthracene (VIII).—The following procedure for obtaining this compound was devised after a large number of attempts to isolate the unstable intermediate, 3-hydroxy-9-methyl-1,2-benzanthracene (VII), in pure form proved unsuccessful. Forty milliliters of purified dioxane was placed in a flask equipped with a condenser and a gas inlet tube and the air in the system was displaced by nitrogen. Hydroquinone (0.10 g.) was then added followed by 2.0 g. of the methoxy compound (VI) and 6 ml. of 48% hydrogen bromide (anal. reag.). The turbid mixture was heated for one hour on the water-bath while nitrogen was continuously introduced under the surface of the liquid. Most of the solvent was distilled from the mixture and the remaining solvent was decanted from the dark green oil which separated; occasionally it was necessary to add a few ml. of water to aid in the separation.

This oil was immediately dissolved in 28 ml. of dioxane in a tube prepared for sealing. Ten grams of sodium bisulfite (anal. reag.), 16 ml. of water and 40 ml. of 28% ammonium hydroxide (anal. reag.) were added. The tube was cooled, sealed, placed in a small electrically heated rocking bomb equipped for temperature control and heated at 180–190° for about 30 hours. By the end of the heating period the hot liquid consisted of only one phase although two had been present originally. Upon cooling the sealed tube, the free amine (VIII) separated as well-defined crystals. These were washed well with water and dried in a vacuum desiccator. This material which melted at 112.1–115.9° and weighed 1.76 g. (93% yield calculated from VI) was entirely satisfactory for conversion to the isocyanate. A sample for analysis was prepared by adding ether, filtering off a little insoluble material, replacing most of the ether by toluene, cooling in a Dry Ice–alcohol-bath and rapidly filtering off the well-formed needles. Upon recooling the filtrate and refiltering a total yield of 65% (calculated from VI) which melted at 116.6–117.4° was obtained.

Anal. Calcd. for $C_{19}H_{15}N$: N, 5.44. Found: N, 5.35.

The small amount of insoluble material filtered from the ether solution of the unpurified amine, as described just above, existed as well-formed yellow needles which decomposed at 270–271°. Determination of the molecular weight by the Rast method gave a value of 496. This suggested the compound is the bis-(9-methyl-1,2-benzanthryl-3) ether for which the calculated mol. wt. is 498.6. Analytical results also agreed satisfactorily.

Anal. Calcd. for $C_{38}H_{26}O$: C, 91.53; H, 5.23. Found: C, 91.30; H, 5.11.

This compound was isolated in only about 0.1% yield. Further support for the proposed structure was obtained when 0.06 g. of the compound was cleaved with hydrobromic acid and subjected to the conditions of the Bucherer reaction in the same general fashion as just described for the methoxy compound (VI). The amine product melted at 116.6–117.4° both alone and when mixed with the amine (VIII) prepared from the methoxy compound. The over-all yield was 34%.

Anal. Calcd. for $C_{19}H_{15}N$: C, 88.68; H, 5.88; N, 5.44. Found: C, 88.74; H, 5.77; N, 5.49.

9-Methyl-1,2-benzanthryl-3-isocyanate (IX).—Ether was added to 0.3 g. of the slightly impure amine (VIII, m.p. 112.1–115.9°), a small amount of insoluble material was filtered off and a little benzene was added. The solution was warmed and treated with 2.65 g. of phosgene dissolved in 11 ml. of toluene. A precipitate appeared which dissolved upon heating the mixture under reflux for about ten minutes. Most of the solvent was removed by distillation at atmospheric pressure and petroleum ether (30–60°) was added until a slight turbidity appeared. Upon cooling, 0.238 g. (73%) of needles which melted at 63.0–64.2° was obtained.

Anal. Calcd. for $C_{20}H_{13}ON$: C, 84.77; H, 4.62; N, 4.94. Found: C, 84.39; H, 4.84; N, 4.82.

Ethyl 9-methyl-1,2-benzanthryl-3-carbamate (X) was prepared as a derivative. A solution of 0.04 g. of the isocyanate in 10 ml. of absolute alcohol was heated under reflux for ten hours. Six ml. of toluene was added and the solution was washed with water and dried over magnesium sulfate. Upon adding petroleum ether (30–60°) and cooling, 0.03 g. (65%) of pale yellow needles which melted at 174.2–174.9° was obtained.

Anal. Calcd. for $C_{22}H_{19}O_2N$: N, 4.25. Found: N, 4.19.

3-Methoxy-9,10-dimethyl-1,2-benzanthracene (VIA).—A solution of 0.24 mole (69 g.) of the crude anthrone (IV) in 1500 ml. of benzene was slowly added to a solution of 0.96 mole of methylmagnesium bromide in 2400 ml. of anhydrous ether. The color changed from dark red to green. After the mixture was heated under reflux for one hour the complex was decomposed with dilute sulfuric acid and ice. The layers were separated and the aqueous layer was extracted with 2:1 benzene–ether. The non-aqueous solutions were combined, washed with water until free of acid and then with saturated sodium chloride solution and dried over magnesium sulfate. The solvents were replaced by toluene and petroleum ether from which the 3-methoxy-9,10-dihydro-9,10-dimethyl-10-hydroxy-1,2-benzanthracene (VA) crystallized as brownish scales. Removal of all the solvent under low pressure gave a total of 65.3 g. (90%) of crude product. Attempts to obtain an analytically pure sample were unsuccessful, possibly because of dehydration to VIA.

When this 65.3 g. of crude VA was heated for about five minutes at 200° dehydration readily occurred. The product (VIA) was best purified *via* chromatographic adsorption applied to the picrate as described above for the monomethyl compound (VI). Upon concentration and cooling of the benzene solution 43.0 g. of lustrous yellow-white plates was deposited; m.p. 129.9–130.9°. The over-all yield for the three steps from the benzoic acid (III) was 62%.

Anal. Calcd. for $C_{21}H_{18}O$: C, 88.06; H, 6.30; CH_3O–, 10.83. Found: C, 88.07; H, 6.41; CH_3O–, 10.79.

3-Amino-9,10-dimethyl-1,2-benzanthracene (VIII A).—Two grams of the methoxydimethyl compound (VIA) was cleaved in exactly the same manner as described above for the monomethyl compound (VI).

The crude 3-hydroxy-9,10-dimethyl-1,2-benzanthracene (VIIA) was subjected to the conditions of the Bucherer reaction as described for VII. Definite crystals were not observed upon cooling the reaction tube. The aqueous dioxane phase was decanted from the red solid or oil phase which contained the amine and extracted with ether. The amine phase was dissolved in the ether extract and the highly fluorescent solution was washed well with water and dried over magnesium sulfate. Twenty ml. of toluene was added, the ether was evaporated on the steam-bath and low boiling (30–60°) petroleum ether was added until the first slight turbidity appeared. Upon cooling 1.27 g. (67% calculated from VIA) of wool-like, bright yellow needles deposited; m.p. 128.9–130.9°.

Anal. Calcd. for $C_{20}H_{17}N$: N, 5.16. Found: N, 5.13.

9,10-Dimethyl-1,2-benzanthryl-3-isocyanate (IXA).—It was not necessary to use the purified amine in this step. The fluorescent dry ethereal solution of the crude amine, prepared from 2 g. of the methoxy compound as just described, was diluted with 40 ml. of benzene. The ether was evaporated from a steam-bath and a solution of 14 g. of phosgene in 65 ml. of toluene was added to the warm benzene solution. The solution was refluxed and the product isolated as described for IX. A 67% yield (calculated from VIA) of yellow needles was obtained. Both this product and one obtained in 68% yield from the purified amine melted at 115.4–115.8°.

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[8] Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Massachusetts, 1941, p. 342.

Anal. Calcd. for $C_{21}H_{15}ON$: C, 84.82; H, 5.08; N, 4.71. Found: C, 84.61; H, 5.33; N, 4.91.

A solution of 0.025 g. of this isocyanate in 25 ml. of absolute alcohol was refluxed for 20 hours. Ethyl 9,10-dimethyl-1,2-benzanthryl-3-carbamate (XA) was isolated in 63% yield as described above for X. The pale yellow needles melted at 113.3–114.1°; a mixture with the isocyanate (IXA) melted considerably lower.

Anal. Calcd. for $C_{23}H_{21}O_2N$: N, 4.07. Found: N, 3.91.

3-Methoxy-9-methyl-10-phenyl-1,2-benzanthracene (XI).—One liter of a benzene solution of crude anthrone (IV) prepared from 25 g. of the substituted benzoic acid (III) was added to 1 l. of an ethereal solution, containing 0.125 mole of phenylmagnesium bromide. The mixture was refluxed 12 hours and the crude tertiary alcohol isolated in the same general fashion as for VA. The product obtained upon dehydration on the hot-plate and purification *via* chromatographic adsorption applied to the picrate, as before, resisted attempts at crystallization. Molecular distillation gave 23 g. (81%, calculated from III) of an orange, glassy solid which had no definite melting point, but which analyzed satisfactorily.

Anal. Calcd. for $C_{26}H_{20}O$: C, 89.62; H, 5.78; CH_3O–, 8.90. Found: C, 89.84; H, 6.04; CH_3O–, 8.93.

3-Methoxy-9-methyl-10-ethyl-1,2-benzanthracene (XII).—This compound was prepared in the same general fashion as described for XI. Crystallization from a large volume of 30–60° petroleum ether gave a 60% yield (calcd. from III) of fine rosettes which melted at 86.4–87.2°.

Anal. Calcd. for $C_{22}H_{20}O$: C, 87.96; H, 6.67; CH_3O–, 10.33. Found: C, 87.97; H, 6.77; CH_3O–, 10.26.

Acknowledgment.—The authors are grateful to Professor N. L. Drake for his helpful interest in this work.

Summary

9-Methyl- and 9,10-dimethyl-1,2-benzanthryl-3-isocyanates have been prepared from α-methoxynaphthalene by nine-step syntheses. Good yields were obtained in each step, the over-all yield being about 28% in each case.

College Park, Maryland Received July 17, 1950

[Contribution from the Laboratory of Organic Chemistry of the University of Wisconsin]

Structure and Hydrogenation of Key Intermediates in the Equilenin Synthesis[1,2]

By William S. Johnson, C. David Gutsche,[3] Ralph Hirschmann[4] and Verner L. Stromberg[5]

In the equilenin synthesis developed in this Laboratory,[1] the product of the pivotal reaction, *viz.*, the condensation of dimethyl succinate with 2-cyano-1-keto-7-methoxy-2-methyl-1,2,3,4-tetrahydrophenanthrene, was formulated as 15-carbomethoxy-14,15-dehydroequilenin methyl ether, I ($R^1 = OCH_3$, $R^2 = H$, $R^3 = CH_3$). This structure was proved conclusively except for the position of the ethylenic bond, which might alternately be located in the 15,16-position, formula II ($R^1 = OCH_3$, $R^2 = H$, $R^3 = CH_3$).[6] The ultraviolet absorption spectrum of this ester has been determined and found to be compatible with the structure I ($R^1 = OCH_3$, $R^2 = H$, $R^3 = CH_3$) on the basis of the high maximum at 323 mμ presumably arising from the extended conjugation in the 6-methoxy-2-naphthylacrylic acid system.[7] Surprisingly the acid, which is obtained in practically quantitative yield by the saponification of I ($R^1 = OCH_3$, $R^2 = H$, $R^3 = CH_3$), has a spectrum (Fig. 1) which is strikingly different from that of the ester in that the high maximum at 323 mμ had vanished. We were, therefore, forced to the conclusion that the bond had shifted from the 14,15- to the 15,16-position during the alkali treatment. This 3-carbon tautomeric shift evidently was essentially complete since the spectrum of the crude saponification product (Fig. 1) showed no indication of the high maximum at 323 mμ. That an isomerization had occurred was further demonstrated by treatment of the acid with diazomethane to produce a new methyl ester, m.p. 136–137°, which was different from the original ester I ($R^1 = OCH_3$, $R^2 = H$, $R^3 = CH_3$), m.p. 170–171°. The spectrum of the lower-melting ester (Fig. 1), moreover, was similar to that of the acid which is now formulated as 15-carboxy-15,16-dehydroequilenin methyl ether, II ($R^1 = OCH_3$, $R^2 = R^3 = H$) instead of the 14,15-dehydro compound.

Analogous behavior was noted in the parent series lacking the ring methoxyl as shown by a comparison of the spectrum of 15-carbethoxy-14,15-dehydro-17-equilenone, I ($R^1 = R^2 = H$, $R^3 = C_2H_5$), with that of the acid obtained on saponification (Fig. 2). Since the latter curve lacks the peak at 309 mμ characteristic of the β-2-naphthylacrylic acid system and resembles closely that of 15,16-dehydro-17-equilenone in which the naphthalene nucleus is not conjugated with the ethylenic bond, the acid is now assigned the structure of 15-carboxy-15,16-dehydro-17-equilenone (II) ($R^1 = R^2 = R^3 = H$).

Similarly 6-methoxy-15-carbomethoxy-14,15-dehydro-17-equilenone[8] (I) ($R^1 = H$, $R^2 = OCH_3$, $R^3 = CH_3$), was converted on saponification to the acid II ($R^1 = H$, $R^2 = OCH_3$, $R^3 = H$) having the bond shifted to the 15,16-position. The spectrum of the acid and its methyl ester differ markedly from that of the starting keto ester, the latter exhibiting absorption at longer wave lengths (Fig. 3), but this difference is not as striking as in the cases described above. The curve of the 15,16-dehydro keto ester resembles very closely that of 6-methoxy-15-carboxy-17-equilenone produced by hydrogenation of II ($R^1 = H$, $R^2 = OCH_3$, $R^3 = H$). This similarity is reasonable only if the double bond of the dehydro acid is in the 15,16-position, because the principal absorption of the isolated O═C—C═C—COOH system as it is contained

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[1] Johnson, Petersen and Gutsche, This Journal, **69**, 2942 (1947).

[2] This work was assisted in part by the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation.

[3] W. A. R. F. postdoctorate fellow, at University of Wisconsin summer 1947. Washington University, St. Louis, Mo.

[4] Sterling-Winthrop Research Institute Fellow at University of Wisconsin 1949–1950. Merck and Co., Inc., Rahway, N. J.

[5] W. A. R. F. research assistant at University of Wisconsin 1949. Weber College, Ogden, Utah.

[6] See footnote 23, ref. 1.

[7] Johnson and Stromberg, This Journal, **72**, 505 (1950).

[8] Hirschmann and Johnson, *ibid.*, **73**, 326 (1951).