containing 17 g. of technical sodium dichromate in 50 ml. of water was added as rapidly as possible with vigorous stirring. After 2 or 3 minutes, the mixture was filtered and the red-brown precipitate was washed with a liter of water and steam distilled. The yellow monomeric product, m.p. 144–145° (lit.[19] m.p. 146.5°), solidified from the steam distillate (51% yield).

Anal. Calcd. for $C_6H_4N_2O_2$: C, 52.94; H, 2.96; N, 20.58. Found: C, 52.98; H, 3.06; N, 20.80.

ψ-*p*-Dinitrosobenzene was prepared from phenol and nitrous acid.[20] Potassium bromide wafers of the initially formed rose colored, apparently polymeric product and the sublimed crystalline green monomer, m.p. 174–175° dec., gave identical absorption in the infrared, 2–16 μ.

The dioxime of *o*-benzquinone was obtained upon alkaline reduction of ψ-*o*-dinitrosobenzene with hydroxylamine.[21] The dioxime of *p*-benzquinone was commercially available.

The directions for the preparation of 3,4,5,6-tetrabromocyclohexenfuroxane (III) were modified.[12] To 150 ml. of carbon disulfide containing 7 g. (0.05 mole) of ψ-1,2-dinitrosobenzene, m.p. 71–72°, 17 g. (0.21 mole) of bromine in 30 ml. of carbon disulfide was added. The reaction mixture was irradiated for three hours with a 275-watt ultraviolet lamp. After evaporation of about half the solvent, 16 g. (70%) of tetrabromocyclohexenfuroxane was collected and washed with cold dilute alcohol. Upon recrystallization from 95% ethanol, the white needles melted at 172–173° (lit.[12] m.p. 170°). The dehydrobromination[12] was effected by adding 15% aqueous potassium hydroxide solution dropwise to 4.5 g. (0.01 mole) of tetrabromocyclohexenfuroxane in ethanol solution. At the end of the addition, the original yellow solution had turned brown. Evaporation of excess solvent permitted the separation of yellow crystals of 3,6-dibromo-ψ-1,2-dinitrosobenzene, 1.8 g. (60%) after recrystallization from ethanol, m.p. 132–133° (lit.[12] m.p. 132°).

3,6-Dibromo-*o*-phenylenediamine was prepared in two ways. The first consisted in adding a small excess of granular tin to a suspension of 0.8 g. (0.0025 mole) of 3,6-dibromo-ψ-1,2-dinitrosobenzene, m.p. 130–131°, in 25 ml. of 6 *N* hydrochloric acid. The reaction mixture was refluxed until reduction was complete (about 40 minutes) and the solution became colorless. Some additional 6 *N* hydrochloric acid was added to dissolve all the diamine hydrochloride. The hot solution was filtered to remove any excess tin and other impurities. Upon cooling, the amine hydrochloride, m.p. 150–155°, was recovered as fine white crystals (0.7 g.), 70% yield. Part of the amine salt was neutralized with a small excess of dilute sodium bicarbonate solution, in a suspension of dilute ethanol. More dilute ethanol was added to dissolve all the free amine, once the neutralization was completed. The diamine was once more recrystallized from dilute ethanol, and poorly defined white crystals, m.p. 95–96° (lit.[22] m.p. 94–95°), were recovered. This amine dissolved in concentrated nitric acid with dark red coloration.

The second method of preparation involved good stirring of a suspension of 0.6 g. (0.002 mole) of 3,6-dibromo-ψ-1,2-dinitrosobenzene in 15 ml. of hydriodic acid, kept at 110–120° for 20 minutes. No reduction occurred below 105–110°. At the end of this period, 20% aqueous sodium bisulfite solution was added slowly to the dark brown reaction mixture until all elemental iodine was reduced and the solution became colorless. After cooling in an ice-bath the yellow crystals of the amine hydroiodide separated and were filtered with suction. These yellow crystals were suspended in about 5 ml. of dilute alcohol, as a dilute solution of sodium bicarbonate was added until the solution became slightly alkaline. More dilute alcohol was added to dissolve all the free amine. After two additional recrystallizations, poorly defined white crystals, m.p. 93–94° were obtained, 0.1 g. (20%).

(19) F. J. Alway and R. A. Gortner, *Ber.*, **38**, 1899 (1905), reported a reduction of *m*-dinitrobenzene with zinc and acetic acid to *m*-phenylenedihydroxylamine followed by oxidation with ferric chloride to *m*-dinitrosobenzene. In our hands this method gave very poor yields.

(20) P. Ruggli and C. Bartusch, *Helv. Chim. Acta*, **27**, 1371 (1944).

(21) T. Zincke and P. Schwarz, *Ann.*, **307**, 39 (1899).

(22) D. F. Calhane and P. M. Wheeler, *Am. Chem. J.*, **22**, 449 (1899).

NEW ORLEANS, LOUISIANA

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF NEW MEXICO]

The Synthesis of 9-Methyl-3,4-benzpyrene and 8,9-Dimethyl-3,4-benzpyrene[1-3]

BY JULES L. ADELFANG[4] AND GUIDO H. DAUB

RECEIVED OCTOBER 29, 1956

3-Keto-1,2,3,11b-tetrahydro-7H-*meso*-benzanthracene (I) underwent a Reformatsky reaction with ethyl bromoacetate, and dehydration of the resulting hydroxy ester followed by hydrolysis produced a mixture of isomeric acids in 83% yield from I. These acids were probably (1,11b-dihydro-7H-*meso*-benzanthrenyl-3-)-acetic acid (II), the predominant isomer, (1,2,3,11b-tetrahydro-7H-*meso*-benzanthrylidene-3)-acetic acid (III) and (4,5-dihydro-6H-*meso*-benzanthrenyl-3)-acetic acid (IV), an abnormal product. Catalytic reduction of II and III produced (1,2,3,11b-tetrahydro-7H-*meso*-benzanthrenyl-3)-acetic acid (V) which underwent the Wilds modification of the Arndt–Eistert synthesis with diazoethane in 89% yield producing β-(1,2,3,11b-tetrahydro-7H-*meso*-benzanthrenyl-3)-isobutyric acid (VI). Cyclization of VI in the presence of anhydrous hydrogen fluoride produced 8-keto-9-methyl-1,2,2a,5,8,9,10,10a-octahydro-3,4-benzpyrene (VII). The ketone VII was reduced by the Meerwein–Ponndorf method or methylated with methylmagnesium iodide producing carbinols which were dehydrated and dehydrogenated to 9-methyl-3,4-benzpyrene and 8,9-dimethyl-3,4-benzpyrene, respectively. This synthesis clarified the conflicting communications reporting the isolation of 9-methyl-3,4-benzpyrene. The new 3,4-benzpyrenes gave ultraviolet absorption spectra similar to the parent hydrocarbon, 3,4-benzpyrene. Samples of these new hydrocarbons will be evaluated for carcinogenic activity at the Northwestern University Medical School, Evanston, Ill.

The isolation of 9-methyl-3,4-benzpyrene (VIII) has been reported by Bergmann[5,6] and Fieser.[7] As part of a program directed toward completing the synthesis of the remaining unknown monomethyl-3,4-benzpyrenes,[8] it was of interest to investigate the conflicting properties reported for the 9-methyl isomer (Bergmann: m.p. 171–172.5°, picrate m.p.

(1) From the thesis to be presented by Jules L. Adelfang to the graduate faculty of the University of New Mexico in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) This investigation was supported in part by a research grant (C-1595) from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(3) Submitted for presentation before the Division of Organic Chemistry at the 131st Meeting of the American Chemical Society, Miami, Florida, April 7–12, 1957.

(4) Graduate Research Assistant, February, 1956, to September, 1956.

(5) E. Bergmann and O. Blum-Bergmann, THIS JOURNAL, **58**, 1678 (1936).

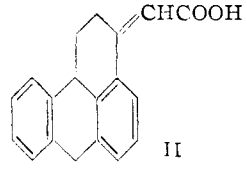
(6) E. Bergmann and F. Bergmann, *ibid.*, **60**, 1805 (1938).

(7) L. F. Fieser and F. C. Novello, *ibid.*, **62**, 1855 (1940).

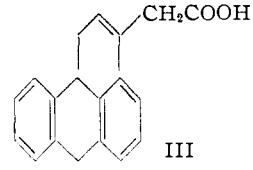
(8) J. L. Adelfang and G. H. Daub, *ibid.*, **77**, 3297 (1955).

172–173°; Fieser: m.p. 147.2–148°). This paper reports the synthesis of 9-methyl-3,4-benzpyrene (VIII) (m.p. 176–177.5° *vac.*, picrate m.p. 201.5–202°), as well as a new dimethyl derivative, 8,9-dimethyl-3,4-benzpyrene (IX), from 3-keto-1,2,3-11b-tetrahydro-7H-*meso*-benzanthracene (I),[9] an intermediate readily available from anthrone.[8]

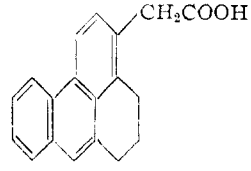
Stobbe condensation of the ketone I with diethyl methylsuccinate gave unsatisfactory results.[10] The hydroxy ester formed by the Reformatsky reaction of the ketone I with ethyl bromoacetate was dehydrated with anhydrous formic acid and then hydrolyzed with dilute alkali to give a mixture of isomeric acids in 83% yield from I. Fractional crystallization of this mixture yielded two unsaturated acids, probably (1,2,3,11b-tetrahydro-7H-*meso*-benzanthrylidene-3)-acetic acid (II) and (1,-11b-dihydro-7H-*meso*-benzanthrenyl-3)-acetic acid (III), the predominant isomer. If the Reformatsky reaction was allowed to proceed for 27 hr. instead of 6.25 hr., fractionation of the resulting mixture of unsaturated acids afforded a 40% yield of a third isomer shown by comparison of ultraviolet absorption spectra[11] to be (4,5-dihydro-6H-*meso*-benzanthrenyl-3)-acetic acid (IV). Catalytic reduction at atmospheric pressure of the mixture containing the unsaturated acids II and III took up 90% of the theoretical amount of hydrogen yielding material which did not react with bromine in carbon tetrachloride. Fractional crystallization of this material gave (1,2,3,11b-tetrahydro-7H-*meso*-benzanthrenyl-3)-acetic acid (V) and a small quantity of the acid IV.



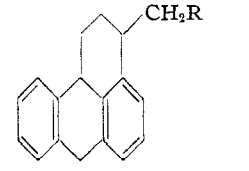
II



III



IV



V, R = COOH

VI, R = CH_3 | CHCOOH

The acid chloride of V, prepared from the acid with phosphorus trichloride, was allowed to react with an excess of diazoethane, and the resulting diazoketone was rearranged as described by Wilds,[12] at 175° in the presence of γ-collidine and benzyl alcohol. Alkaline hydrolysis of the benzyl ester formed in the rearrangement gave β-(1,2,3,11b-tetrahydro-7H-*meso*-benzanthrenyl-3)-isobutyric acid (VI) in an over-all yield of 89% from the saturated acid V.

(9) J. W. Cook, R. S. Ludwiczak and R. Schoental, *J. Chem. Soc.*, 1112 (1950).

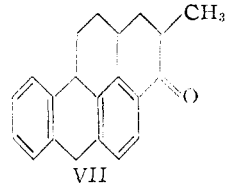
(10) M. D. Barnett, private communication.

(11) R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951, No. 341.

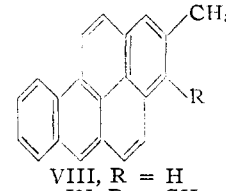
(12) A. L. Wilds and A. L. Meader, *J. Org. Chem.*, **13**, 763 (1948).

Cyclization of the acid VI with anhydrous hydrogen fluoride afforded 8-keto-9-methyl-1,2,2a,-5,8,9,10,10a-octahydro-3,4-benzpyrene (VII) in 73% yield.

Preparation of 9-methyl-3,4-benzpyrene (VIII) was accomplished by reduction of the ketone VII with aluminum isopropoxide in toluene, to 8-hydroxy-9-methyl-1,2,2a,5,8,9,10,10a-octahydro-3,4-benzpyrene which was directly dehydrated and dehydrogenated over palladium–charcoal at 270–340°. The hydrocarbon VIII was obtained in 57% yield from the ketone VII and formed a dark purple picrate derivative.



VII



VIII, R = H
IX, R = CH_3

Reaction of the ketone VII with methylmagnesium iodide gave 8-hydroxy-8,9-dimethyl-1,2,-2a,5,8,9,10,10a-octahydro-3,4-benzpyrene which was dehydrated and dehydrogenated over a palladium–charcoal catalyst at 270–340°, affording 8,9-dimethyl-3,4-benzpyrene (IX) in 72% over-all yield. The hydrocarbon IX formed a dark brown picrate derivative.

The ultraviolet absorption curves for 9-methyl-3,4-benzpyrene (VIII) and 8,9-dimethyl-3,4-benzpyrene (IX) substantiate the presence of the parent ring system in these new hydrocarbons.

Samples of these hydrocarbons are being tested for carcinogenic activity at Northwestern University Medical School under the direction of Dr. D. Warren Stanger.

Experimental[13]

The Reformatsky Reaction on 3-Keto-1,2,3,11b-tetrahydro-7H-*meso*-benzanthracene (I).—Thirty-five grams (0.15 mole) of the ketone I was dissolved in an anhydrous mixture of 700 ml. of C.P. benzene and 700 ml. of C.P. ether in a three-liter three-necked flask equipped with ground glass joints, fitted with a mercury sealed Hershberg stirrer, a condenser fitted with a drying tube and a glass stopper. Initially the apparatus had been flame-dried and swept with nitrogen. After the addition of 90 g. of amalgamated zinc,[14] 55 ml. of ethyl bromoacetate (Eastman Kodak Co. 995) and a trace of iodine, the mixture was refluxed for 6.25 hr. After 3.5 hr. a tan colored complex separated from the reaction mixture and at that time an additional 45 g. of amalgamated zinc and 22 ml. of ethyl bromoacetate were added. The reaction mixture was hydrolyzed at room temperature with a solution of 35 ml. of concentrated hydrochloric acid in 350 ml. of water. The organic layer was washed with water and dried over anhydrous sodium sulfate. Removal of the benzene–ether mixture under reduced pressure left a light red oil which was dehydrated with 100 ml. of anhydrous formic acid by warming on a steam-bath for five minutes. The formic acid was removed under reduced pressure and the remaining oil was refluxed for 2 hr. with 42 g. of sodium hydroxide in 770 ml. of water. The alkaline solution was extracted with a mixture of ether and benzene, and acidified, producing a quantitative yield of crude acidic material as a light brown granular solid, m.p. 146–

(13) All melting points are uncorrected.

(14) Twenty mesh zinc (J. T. Baker C.P.) was amalgamated by the method described by Kolthoff and Sandell, "Textbook of Quantitative Inorganic Analysis," The Macmillan Co., New York, N. Y., 1948, p. 598. The freshly amalgamated zinc was washed with acetone and benzene and stored under benzene before use.

151°. Two crystallizations of the crude acid from ethyl acetate afforded 30.6 g. of a mixture of isomeric acids, m.p. 151–160°. An additional 3.9 g., m.p. 149–153°, of the mixture of isomers was obtained from the mother liquors to make the total yield 34.5 g. (83%). A sample of the isomer mixture was fractionally crystallized from methyl alcohol. A small quantity of (1,2,3,11b-tetrahydro-7H-*meso*-benzanthrylidene-3)-acetic acid (II) crystallized as needles, m.p. 162–163°. The predominant isomer (1,11b-dihydro-7H-*meso*-benzanthrenyl-3)-acetic acid (III) crystallized as granules, m.p. 164–166°.

Anal. Calcd. for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84. Found for II: C, 82.60; H, 5.82. Found for III: C, 82.41; H, 5.90.

Ultraviolet Absorption Spectra.—The ultraviolet absorption spectra of the unsaturated acids II and III in 95% ethanol were measured with a model DU Beckman spectrophotometer. Maxima and (log ϵ) values are: II, 274 mμ (4.06), 333 mμ (3.28) and 350 mμ (3.21); III, 2.62 mμ (3.91), 333 mμ (3.39) and 350 mμ (3.32).

(1,2,3,11b-Tetrahydro-7H-*meso*-benzanthrenyl-3)-acetic Acid (V).—At atmospheric pressure, 27.6 g. (0.10 mole) of the purified acid mixture, m.p. 151–160°, dissolved in 500 ml. of absolute alcohol, was reduced in the presence of 0.2 g. of Adams catalyst. After one day, at room temperature, when 90% of the theoretical amount of hydrogen had been taken up, the solution was filtered and concentrated. The last traces of ethanol were removed by azeotropic distillation with benzene. Concentration of the benzene solution afforded 23.6 g. of a mixture of acids which did not react with bromine in carbon tetrachloride.

Fractional crystallization of this mixture from methyl alcohol yielded two components. Recrystallization of the more insoluble fraction from methyl alcohol and then from ethyl acetate provided an analytical sample of an acid shown by its ultraviolet absorption spectrum to be (4,5-dihydro-6H-*meso*-benzanthrenyl-3)-acetic acid (IV), as needles, m.p. 218–220° (vac.).

Anal. Calcd. for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84. Found: C, 82.82; H, 5.91.

The predominant component was crystallized twice from ethyl acetate producing an analytical sample of (1,2,3,11b-tetrahydro-7H-*meso*-benzanthrenyl-3)-acetic acid (V), as irregular prisms, m.p. 195–196.5°.

Anal. Calcd. for $C_{19}H_{18}O_2$: C. 81.99; H, 6.52. Found: C, 82.11; H, 6.28.

Ultraviolet Absorption Spectra.—The ultraviolet absorption spectrum of (4,5-dihydro-6H-*meso*-benzanthrenyl-3)-acetic acid (VI) in 95% ethanol was measured with a model DU Beckman spectrophotometer. Maxima and (log ϵ) values are: 260 mμ (4.77), 282 mμ (4.13), 290 mμ (4.01), 303 mμ (4.05), 339 mμ (3.11) and 356 mμ (3.06).

β-(1,2,3,11b-Tetrahydro-7H-*meso*-benzanthrenyl-3)-isobutyric Acid (VI).—To 7.78 g. (0.028 mole) of (1,2,3,11b-tetrahydro-7H-*meso*-benzanthrenyl-3)-acetic acid (V), m.p 195–196.5°, dissolved in 70 ml. of anhydrous C.P. benzene was added 1.8 ml. (0.020 mole) of phosphorus trichloride (J. T. Baker, C.P.), and the mixture was refluxed for 1 hr. and 40 minutes. The warm solution of the acid chloride was filtered, and the benzene and excess phosphorus trichloride were removed under reduced pressure.

Diazoethane was prepared as described by Wilds[12] in an all-glass apparatus fitted with a trap cooled to 0° containing anhydrous ether. To a flask containing 18.2 g. of potassium hydroxide dissolved in 70 ml. of *n*-propyl alcohol and 70 ml. of anhydrous ether, 18.2 g. of N-nitroso-N-ethylurethan in 56 ml. of anhydrous ether was added with stirring over a period of 5 minutes while the reaction mixture was maintained at 50°. Distillation was continued at 50° until the distillate was colorless; this required the addition of 150 ml. of anhydrous ether.

The acid chloride prepared above was dissolved in 70 ml. of C.P. anhydrous benzene and added dropwise to the diazoethane solution which had been cooled to −20° in a Dry Ice–acetone-bath. The addition required 15 minutes and was accompanied by the evolution of nitrogen. After allowing the reaction mixture to stand at −20° for an additional 15 minutes, the ether and benzene were removed under reduced pressure, The remaining highly viscous, yellow diazoketone was dissolved in a mixture of 28 ml. of benzyl alcohol and 28 ml. of γ-collidine and placed in a bath preheated to 175°. After a short induction period, nitrogen was evolved vigorously. The reaction was complete in five minutes, and the mixture was cooled and neutralized with 10% hydrochloric acid. Ether was added and the organic layer was washed with 10% hydrochloric acid and water. The ether was removed under reduced pressure and the remaining benzyl ester was refluxed for 2.5 hr. with a mixture of 42 ml. of methyl alcohol and 42 ml. of 45% aqueous potassium hydroxide. The methyl alcohol was removed under reduced pressure, and the reaction mixture was acidified. The crude acid was dissolved in a mixture of ether and benzene and washed with water. The acidic material was extracted with sodium carbonate solution and acidification yielded a tan, viscous semi-solid. An ether–benzene solution of this material was washed with water and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure yielded 7.6 g. (89%) of β-(1,2,3,11b-tetrahydro-7H-*meso*-benzanthrenyl-3)-isobutyric acid (VI) as a viscous, yellow oil.

The above oily mixture of isomers was triturated with 60–90° petroleum ether and then with cyclohexane, and the remaining solid was recrystallized from benzene. Two further recrystallizations from ethyl acetate provided an analytical sample of one of the isomeric β-(1,2,3,11b-tetrahydro-7H-*meso*-benzanthrenyl-3)-isobutyric acids (VI) as colorless needles, m.p. 181.5–183°.

Anal. Calcd. for $C_{21}H_{22}O_2$: C, 82.31; H, 7.24. Found: C, 82.77; H, 7.12.

8-Keto-9-methyl-1,2,2a,5,8,9,10,10a-octahydro-3,4-benzpyrene (VII).—Cyclization of 1.00 g. (0.00326 mole) of β-(1,2,3,11b-tetrahydro-7H-*meso*-benzanthrenyl-3)-isobutyric acid (VI), m.p. 180.5–183°, was accomplished with 10 ml. of anhydrous hydrogen fluoride. The crude ketone was taken up in benzene, washed with water and sodium carbonate solution and dried over anhydrous sodium sulfate. The benzene solution was passed through an alumina column, and the solid ketone obtained by concentration of the benzene eluents was crystallized from methyl alcohol affording 0.69 g. (73% yield) of **8-keto-9-methyl-1,2,2a,5,8,9,10,10a-octahydro-3,4-benzpyrene (VII)** as colorless needles, m.p. 135.5–137°. Recrystallization of VII from methyl alcohol yielded an analytical sample, m.p. 135.5–137°.

Anal. Calcd. for $C_{21}H_{20}O$: C, 87.45; H, 6.99. Found: C, 87.54; H, 7.05.

9-Methyl-3,4-benzpyrene (VIII).—Reduction of 3.8 g. (0.0132 mole) of oily ketone VII obtained from cyclization of the crude acid VI, was carried out with 6.0 g. (0.0294 mole) of aluminum isopropoxide and 100 ml. of C.P. toluene in a 200-ml. round bottom flask fitted with a Hahn condenser. After 24 hr. of intermittent distillation, the distillate gave a negative test with 2,4-dinitrophenylhydrazine reagent. The reaction mixture then was treated with 15 ml. of concentrated hydrochloric acid in 60 ml. of water, and after addition of benzene and ether the organic layer was washed with water and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure yielded **8-hydroxy-9-methyl-1,2,2a,5,8,9,10,10a-octahydro-3,4-benzpyrene** as a viscous oil.

The crude alcohol was dehydrated and dehydrogenated over 0.5 g. of 10% palladium–charcoal in an apparatus suggested by Fieser.[15] After 1.25 hr. at 270–340°, 65% of the theoretical amount of hydrogen was given off. After cooling, the hard cake was dissolved in benzene and the solution filtered. The benzene solution was chromatographed through alumina, and the material obtained by concentration of the eluents was crystallized from ethyl acetate producing 1.65 g. of **9-methyl-3,4-benzpyrene (VIII)** as small yellow needles, m.p. 176–177° (vac.). The mother liquors yielded an additional 0.33 g. of VIII, m.p. 175–176.5° (vac.), making the total yield 1.99 g. (57% from VII). An analytical sample, m.p. 176–177.5° (vac.), was prepared by crystallization from ethyl acetate.

Anal. Calcd. for $C_{21}H_{14}$: C, 94.70; H, 5.30. Found: C, 94.30; H, 5.49.

A picrate of VIII was prepared using a saturated solution of picric acid in benzene. Crystallization of the picrate from benzene yielded dark purple needles, m.p. 201.5–202°. Analysis of two different picrate samples indicated a definite

(15) L. F. Fieser, "Experiments in Organic Chemistry," 2nd Ed., D. C. Heath and Co., New York, N. Y., 1941, p. 462.

picric acid:hydrocarbon ratio not in agreement with the expected equimolal ratio.

Anal. Calcd. for $C_{27}H_{17}O_7N_3$: C, 65.45; H, 3.46. Found: C, 67.05, 67.02; H, 3.63, 3.68.

The over-all yield of 9-methyl-3,4-benzpyrene from purified (1,2,3,11b-tetrahydro-7H-*meso*-benzanthrenyl-3)-acetic acid (V) was 38%. When the crude V, m.p. 150–200°, was carried through the reaction sequence described above without isolation of the acid VI or the ketone VII, the over-all yield was reduced to about 15% and pure 9-methyl-3,4-benzpyrene could only be obtained through the picrate.

8,9-Dimethyl-3,4-benzpyrene (IX).—A Grignard reagent was prepared in the usual manner from 0.24 g. (0.01 g. atom) of magnesium and 2.3 g. (0.016 mole) of methyl iodide in 20 ml. of absolute ether. The ketone VII, 0.63 g. (0.0022 mole), m.p. 135.5–137°, dissolved in 20 ml. of anhydrous benzene was added dropwise to the Grignard solution. After standing at room temperature for 2.5 hr., the reaction mixture was hydrolyzed with dilute hydrochloric acid. The organic layer was washed with water and dried over anhydrous sodium sulfate. Removal of the solvent left **8-hydroxy-8,9-dimethyl-1,2,2a,5,8,9,10,10a-octahydro-3,4-benzpyrene** as a viscous yellow oil.

The crude alcohol was dehydrated and dehydrogenated by heating with 0.1 g. of 10% palladium–charcoal at 270–340° for 0.5 hr. during which time about 65% of the theoretical amount of hydrogen was evolved. After cooling, the hard cake was dissolved in boiling benzene and the solution filtered to remove the catalyst. The crude hydrocarbon was chromatographed through an alumina column and concentration of the eluents yielded 0.39 g. of **8,9-dimethyl-3,4-benzpyrene (IX)** as yellow needles, m.p. 214.5–217° (vac.). The mother liquors yielded an additional 0.05 g. of hydrocarbon, m.p. 214.5–216° (vac.), making the total yield 0.44 g. (72% from VII). An analytical sample, m.p. 214.5–216° (vac.), was prepared by crystallization from ethyl acetate followed by sublimation at reduced pressure.

Anal. Calcd. for $C_{22}H_{16}$: C, 94.25; H, 5.75. Found: C, 93.89; H, 5.97.

A picrate of IX was prepared using a saturated solution of picric acid in benzene. Crystallization of the picrate from benzene yielded dark brown needles, m.p. 217.5–219°.

Anal. Calcd. for $C_{28}H_{19}O_7N_3$: C, 66.01; H, 3.76. Found: C, 65.90; H, 3.57.

Ultraviolet Absorption Spectra.—The ultraviolet absorption spectra of 9-methyl- and 8,9-dimethyl-3,4-benzpyrene in 95% ethanol were measured with a model DU Beckman recording spectrophotometer. Maxima and (log ϵ) values are: 9-methyl-3,4-benzpyrene (VIII), 259 mμ (4.62), 268 mμ (4.72), 287 mμ (4.68), 301 mμ (4.74), 369 mμ (4.40) and 390 mμ (4.47); 8,9-dimethyl-3,4-benzpyrene (IX), 259 mμ (4.64), 270 mμ (4.69), 291 mμ (4.64), 304 mμ (4.76), 372 mμ (4.40) and 392 mμ (4.45).

ALBUQUERQUE, NEW MEXICO

[CONTRIBUTION FROM ABBOTT LABORATORIES]

Muscle-relaxing Compounds Derived from 1,4-Dichloro-2-butene[1]

BY BRUCE W. HORROM AND HAROLD E. ZAUGG

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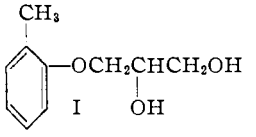
Several aryloxy and alkoxy butanediols were synthesized for testing as muscle-relaxants. These compounds were all derived from 1,4-dichloro-2-butene. The methods of their preparation and their physical constants are reported.

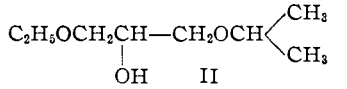
Many derivatives and analogs of the glycerol ethers have been made[2–5] and studied[6–9] for their muscle-relaxing properties.

In the aromatic series, mephenesin (I) remains one of the most useful compounds studied although



I

fairly short acting. In the aliphatic series, 3-ethoxy-1-isopropoxy-2-propanol (II) is less potent



II

than mephenesin but more prolonged in its action.[8]

It has been suggested[7] that muscle relaxant activity in this series depends on a favorable oil-water partition coefficient. Riley[10] has also indicated that the short duration of action of mephenesin-like drugs may be due to the rapid metabolism of these compounds through the oxidation of the terminal primary hydroxyl group.[11] It was felt that the introduction of an alkoxymethyl group into the glycerol side chain of the compounds of mephenesin-type might slow their metabolic rates of destruction without unfavorably affecting their partition coefficients, thereby possibly producing drugs of prolonged duration of effect. Lott[12] has reported that the aryloxybutanediols of the type prepared by Yale,[4] *et al.*, are very insoluble in water. We have found that the introduction of a methoxyl group into the ω-position of the butane side chain results in compounds of greater water solubility. The solubilities of several compounds in Table I were determined in water at 25°. They are as follows: compound 5, 1.83%; compound 6, 5.25%; compound 11, 0.21%; and compound 12, 0.74%. It is interesting to note that compound 12 which had about the same solubility as mephenesin was the most active of these four compounds.

(1) Presented before the Division of Medicinal Chemistry, 128th National American Chemical Society Meeting, Minneapolis, Minn., September 11–16, 1955.

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(3) K. E. Marple, E. C. Shokal and T. W. Evans, U. S. Patent 2,380,185.

(4) H. L. Yale, E. J. Pribyl, W. Braker, F. H. Bergeim and W. A. Lott, THIS JOURNAL, **72**, 3710 (1950).

(5) B. J. Ludwig, W. A. West and W. E. Currie, *ibid.*, **74**, 1935 (1952).

(6) F. M. Berger, *J. Pharmacol. & Exper. Therap.*, **93**, 470 (1948).

(7) C. H. Hine, B. E. Christensen, F. J. Murphy and H. Davis, *ibid.*, **97**, 414 (1949).

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(10) R. F. Riley, THIS JOURNAL, **72**, 5712 (1950).

(11) The work of Riley has been confirmed recently by Ludwig, *et al.* [B. J. Ludwig, H. Luts and W. A. West, *ibid.*, **77**, 5751 (1955)].

(12) W. A. Lott, *Trans. N. Y. Acad. Sci.*, [2] **11**, 1 (1948).