The tube was chilled in liquid nitrogen, opened, the excess chlorine allowed to evaporate, and the product extracted with petroleum ether (b.p. 35–37°). The extract, after decolorization with Norite, was concentrated to 75 ml., chilled and filtered; the white tabloids were recrystallized from benzene–methanol to give 8.2 g. (62%) of compound II, m.p. 167–168°; no depression of m.p. was observed on admixture with an authentic sample of II prepared by direct chlorination of bicyclopentyl. The infrared spectra of compound II as prepared by both procedures were identical.

Anal.[6] Calcd. for $C_{10}Cl_{14}$: C, 19.51; Cl, 80.49. Found: C, 19.41; Cl, 79.91.

At lower temperatures, chlorine appeared to have no effect on I. Thus, when chlorine gas was passed into a solution of I in carbon tetrachloride in the presence of actinic light for 48 hr. at 25°, no reaction occurred, the starting material being recovered.

Pyrolysis of II. A. At 250–300°.—Compound II (15 g., 0.024 mole) was placed in a Pyrex tube 1.5 × 10 cm. which was equipped with a side arm leading into a cooled receiver. With the system partially evacuated (25 mm.) the temperature of the tube and contents was raised gradually in a Woods metal-bath to 300° and so maintained for 2 hr. The liquid collected in the receiver was distilled, b.p. 83–86° (2 mm.), giving 6.7 g. (50%) of hexachlorocyclopentadiene, $n^{20}D$ 1.5657. Chlorine was detected in the exhaust gases from the receiver. The pyrolysis residue was dissolved in 100 ml. of hot benzene; after decolorization with Norite, the solution was diluted with an equal volume of methanol and chilled giving 5.9 g. of II, m.p. and mixed m.p. 165–166°.

When the experiment was repeated at 275°, pyrolysis took place much less readily, and after 3 hr. only the faint odor of hexachlorocyclopentadiene was detected in the product receiver. Of 10 g. of II used, 9.1 g. was recovered. A sample of the recovered crystals, m.p. 161–164°, was dissolved in chloroform and the infrared spectrum of the solution carefully examined for foreign absorption, none being noted.

Using a modified procedure, II (10 g., 0.016 mole) was slowly heated at atmospheric pressure in a cold finger (Dry Ice) sublimator to 250° and the temperature maintained for 3 hr. A white sublimate, 2 g., was shown to be II, m.p. 166–167°. The residue, 7.5 g., crystallized on cooling to nearly pure II, m.p. 163–166°. Infrared analysis of this solid likewise showed no foreign material present.

B. **At 425°.**—Compound II (10 g., 0.016 mole) was sealed in a carius tube at 1 mm. pressure. The tube was heated rapidly in an electric furnace to 375° and then during the next 4.5 hr., to 425°. After cooling, the tube was opened and the solids extracted with petroleum ether (b.p. 60–70°). Decolorization and chilling of the extracts gave 5.2 g. of hexachlorobenzene, m.p. 222°. On admixture with an authentic sample, m.p. 224–225°,[7] the m.p. was undepressed and the infrared spectra of the two substances (in chloroform) were identical.

Acknowledgment.—The authors express their appreciation to the Hooker Electrochemical Co. for financial assistance during this research.

(6) Analysis by Mrs. T. P. Yeh, Purdue University.

(7) E. H. Huntress, "Organic Chlorine Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 477.

WEST LAFAYETTE, INDIANA

[CONTRIBUTION FROM THE INSTITUTE FOR CANCER RESEARCH AND THE LANKENAU HOSPITAL RESEARCH INSTITUTE]

Functional Derivatives of 1,2-Benzanthracene[1]

BY RICHARD M. PECK

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The 6- and 2′-methoxy derivatives of 9,10-dimethyl-1,2-benzanthracene and 7-methoxy-10-methyl-1,2-benzanthracene have been prepared. The 6- and 7-methoxy groups have been converted by hydrolysis, Bucherer reaction, and reaction with phosgene to the corresponding isocyanates.

Since water-soluble derivatives of 9,10-dimethyl-1,2-benzanthracene and other carcinogens have shown interesting biological properties,[2a] it was thought desirable to attach the solubilizing group through a position less vital[2b] to carcinogenic potential than the 3-, 9- or 10-positions. Syntheses were directed toward obtaining the 2′-, 6- and 7-methoxy compounds and thence, through hydrolysis, Bucherer reaction, and reaction with phosgene, the corresponding isocyanates, which permit attachment of the carcinogen to a variety of amino acids and proteins.[3]

Starting materials for the 6- and 7-compounds were the two isomeric keto acids I and II obtained by the reaction of 1,2-naphthalic anhydride either with *p*-methoxyphenylmagnesium bromide or with anisole under Friedel–Crafts conditions. It was found that slow precipitation from a salt solution of a mixture of I and II gave practically pure II until the ratio I:II, as their salts in the mother liquor, was quite high. The remaining acids on crystallization from acetone–benzene gave almost pure I. The ratio of the two compounds produced through one route was approximately the inverse of that from the other reaction. As one would expect from similar syntheses,[4] the predominant product of the Grignard synthesis was the β-keto-α-naphthoic acid (I); the Friedel–Crafts reaction was apparently not influenced by steric effects. During the proof of structure necessary to differentiate between the isomers, it was found that the degradation product III, both derived from II and independently synthesized, has been incorrectly reported in several places in the literature.[5] On examination of the two available references to III it was noted (1) that in either case such strenuous conditions were employed that the possibility existed of methoxyl removal, (2) that a methoxyl analysis was not reported for the compound and (3) that the percentages of carbon and hydrogen in III and its phenolic derivative were too close to allow differentiation. The isomeric *p*-methoxyphenyl

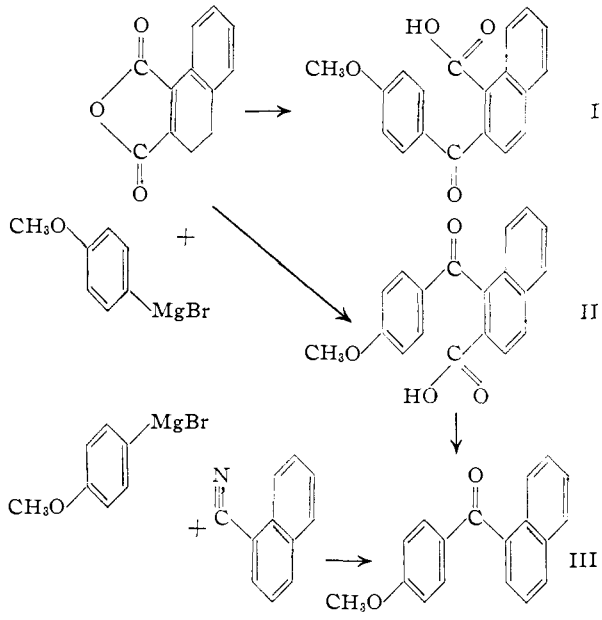
(1) Supported by an institutional grant from the American Cancer Society.

(2) (a) H. J. Creech, *Cancer Research*, **12**, 557 (1952); E. U. Green, *ibid.*, **14**, 591 (1954); (b) A. Pullman, *Ann. chim.*, **2**, 5 (1947); R. Daudel, *Bull. Cancer*, 110 (1948); H. H. Greenwood, *Brit. J. Cancer*, **5**, 441 (1951).

(3) R. M. Peck, H. J. Creech and G. L. Miller, THIS JOURNAL, **75**, 2364 (1953).

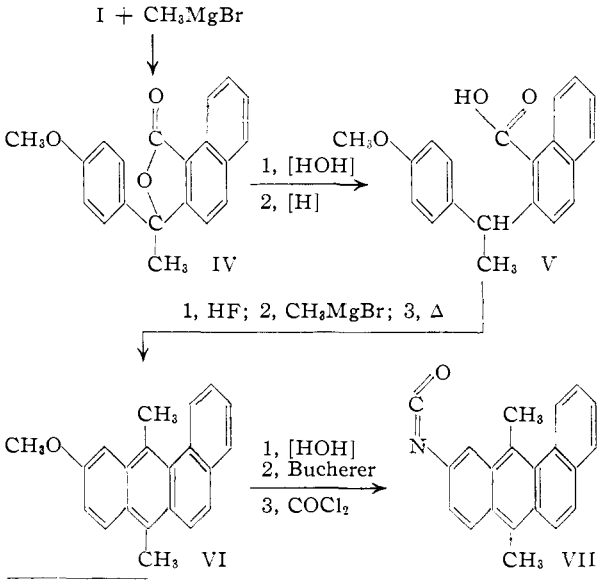
(4) M. S. Newman and P. H. Wise, THIS JOURNAL, **63**, 2109 (1941); M. S. Newman and C. D. McCleary, *ibid.*, **63**, 1542 (1941).

(5) (a) G. Baddeley, *J. Chem. Soc.*, S99 (1949); his reference to Meister, Lucius and Bruning, British Patent 234,173 (1924); (b) F. Unger, *Ann.*, **504**, 285 (1933).



naphthyl ketone was similarly obtained by degradation of I and by synthesis.

Compound I, by a series of reactions paralleling the synthesis of 9,10-dimethyl-1,2-benzanthryl 3-isocyanate by Smith, Pratt and Creech,[6] gave 9,10-dimethyl-1,2-benzanthryl 7-isocyanate. However, we were unable either to isolate a pure compound from the treatment of II with methyl Grignard (chloride or bromide) or to obtain an acidic product by subjecting the oily product from that Grignard reaction to the action of zinc and alkali. Therefore, an attempt was made, by direct reduction of II, to obtain a methylene rather than an ethylidene bridge and thus obtain a monomethylmethoxybenzanthracene. It was found that the prolonged action of zinc and alkali on the hindered ketonic group gave a mixture from which a small yield of the desired *p*-methoxybenzylnaphthoic acid was



(6) W. M. Smith, E. F. Pratt and H. J. Creech, THIS JOURNAL, **73**, 319 (1951).

obtained; the rest of the synthesis proceeded satisfactorily. Also isolated from the zinc and alkali reduction was a hydroxy acid which was not the carbinol intermediate, but rather a hydrogenated derivative of it apparently containing an extra pair of hydrogens in both the phenyl and naphthyl skeleton. This possibly occurred by 1,4- (or 1,6-) additions to the conjugated carbonyl followed by tautomeric shifts before the carbonyl itself was finally reduced by a 1,2-addition of hydrogen.

The 2′-methoxy-9,10-dimethyl-1,2-benzanthracene was produced by the same scheme of synthesis as the 7-methoxy compound starting with 7-methoxy-1,2-naphthalic anhydride and phenylmagnesium bromide. It was not necessary to separate the isomeric mixture of acids produced in the first step since both yielded the same end product. However, only one chemical individual was isolated from the next reaction, presumably the lactone derived from the β-keto-α-naphthoic acid, which should predominate in the mixture from the Grignard reaction,[4] and which should undergo the reaction with methylmagnesium bromide in better yield (by analogy with compounds I and II). However, this work does not rigidly differentiate between the two intermediate compounds and their respective positional isomers. So far, successful conditions for the synthesis of the 2′-isocyanate have not been found; the difficulty lies in the resistance of the 2′-methoxy group to hydrolysis under conditions safe for the rest of the molecule.

Experimental

2-(*p*-Anisoyl)-1-naphthoic Acid (I) and 1-(*p*-Anisoyl)-2-naphthoic Acid (II). (a) Grignard.—To a refluxing, stirred suspension of 5.8 g. (0.25 mole) of magnesium in 300 ml. of dry ether was added slowly 41 g. (0.22 mole) of *p*-bromoanisole. The mixture was refluxed overnight, filtered through glass wool, diluted with ether to 500 ml. and added, over a period of one hour, to a stirred solution of 40 g. (0.20 mole) of 1,2-naphthalic anhydride in 600 ml. of benzene. After an additional hour of stirring, hydrolysis was accomplished with ice and hydrochloric acid, with 175 ml. of acetone being added to help dissolve the products. After the disappearance of an oily, partially hydrolyzed phase, the organic layer, containing some crystalline product in suspension, was separated and washed. The combined aqueous layers were extracted with benzene–acetone and the total suspension of product in organic solvent was extracted with three 350-ml. quantities of *N*/3 sodium hydroxide. After addition of 200 ml. of acetone to the extracts and treatment with decolorizing carbon, the product was precipitated by dropwise addition of dilute hydrochloric acid, with stirring, giving 36 g. (58%) of a mixture of I and II, m.p. 160–190°, neut. equiv. = 309. This product was dissolved in 200 ml. of acetone, treated with decolorizing carbon and filtered twice. The solution was refluxed while 700 ml. of filtered benzene was added. The solution was cooled without agitation until crystallization was first observed, then the mixture was swirled for about five minutes in an ice-bath, filtered immediately and the crystals were washed with benzene and petroleum ether. The yield of I of melting point 179.5–181° was 18.0 g. (29%). A second crop of 5.5 g., obtained in the same way after concentration of solvent, melted at 166–168.5°, and was set aside for further purification.

The remainder (11 g.), recovered from the solution by concentration and addition of petroleum ether, was dissolved in 300 ml. of acetone, neutralized to phenolphthalein and diluted with water to 700 ml. The resultant clear solution was stirred while dilute hydrochloric acid was added dropwise (seeding with previously isolated II). After crystallization had begun, 60 ml. of *N*/3 acid was added dropwise, yielding a granular precipitate which weighed 7.1 g. (11.5%), m.p. 212–216° with previous softening. Manipulation of

second crops gave an additional 2.5 g. of I, m.p. 179.5–181°, and 5.0 g. of unresolved mixture. A 33% yield of I and an 11.5% yield of II were obtained. A previously obtained sample of I, m.p. 178–179°, neut. equiv. 304 was analyzed. *Anal.* Calcd. for $C_{19}H_{14}O_4$: C, 74.5; H, 4.61. Found: C, 74.68, 74.79; H, 4.96, 5.01. A previously obtained sample of II, m.p. 217.4–218.4°, neut. equiv. 306.5 was analyzed. Found: C, 74.46, 74.53; H, 4.81, 4.83.

(b) **Friedel–Crafts.**—A mixture of 61.5 g. (0.57 mole) of anisole, 99 g. (0.50 mole) of 1,2-naphthalic anhydride and 400 ml. of tetrachloroethane was stirred while 135 g. of anhydrous aluminum chloride was added in portions, the temperature being maintained at 15 ± 2° by a cooling bath. The mixture was maintained at that temperature with stirring for six hours and without stirring overnight. Hydrolysis was accomplished by stirring with ice and hydrochloric acid. A 23-g. portion of the product crystallized from the mixture and was filtered, washed and dried. It apparently consisted, to an appreciable extent, of I, manipulation yielding 7.2 g. of m.p. 180–181°.

The two-phase filtrate was separated and to the organic phase, plus several small tetrachloroethane extracts of the aqueous layer, were added water and excess sodium carbonate and the tetrachloroethane removed by steam distillation. The residual salt mixture was filtered and poured into a mixture of 200 ml. of water, 200 ml. of acetone and 150 ml. of hydrochloric acid. The mixed acids crystallized and were filtered and dried, yielding 101 g. of product which was dissolved in 700 ml. of acetone, treated with decolorizing carbon and filtered. About 1 liter of water was added and the solution was neutralized to phenolphthalein with 0.5 *N* sodium hydroxide. Careful precipitation of II from the filtered solution by dropwise addition of dilute acid gave a first crop of 10 g., m.p. 215–218°, a second crop of 16 g., m.p. 217–219°, and third and fourth crops totaling 17 g. and melting at 217–220°. Further acidification gave 18 g. of a mixture melting below 160°. Crystallization from acetone–benzene of this material together with material from mother liquors from isolation of the 7.2 g. of I mentioned above yielded two crops of I totaling 11.5 g. A final crop of unresolved mixed acids weighed 8.9 g. The isolated yield of I was 12% and of II was 28%; the products from this reaction and from the Grignard were identical.

***p*-Methoxyphenyl β-Naphthyl Ketone; Proof of Structure of 2-(*p*-Methoxyphenyl)-1-naphthoic Acid.**—A suspension, under nitrogen, of 2.7 g. of magnesium in 250 ml. of dry ether was stirred and refluxed while 18.7 g. (0.10 mole) of *p*-bromoanisole in an equal volume of ether was added dropwise (2 millimoles of methyl Grignard was added initially to start the reaction). After addition was complete, the mixture was stirred and refluxed for one hour; a solution of 15.3 g. (0.10 mole) of β-naphthonitrile in 100 ml. of benzene was added as rapidly as control of the reaction would permit. After refluxing an additional hour, the mixture was poured on ice and hydrochloric acid. The intermediate ketimine hydrochloride separated as an oil which later crystallized. It was boiled with water and the ketonic product extracted with benzene. The benzene solution was washed with water, treated with decolorizing carbon, concentrated, and the residue distilled *in vacuo*. The product, b.p. 179° (90 μ)–171° (50 μ), weighed 15.1 g. (57.5%). One crystallization from benzene–petroleum ether gave 14 g., m.p. 91–92°; the compound was identical with that obtained as follows: A mixture of 0.40 g. of the isomer I obtained from the above described Friedel–Crafts and Grignard reactions, together with a small amount of its cupric salt,[4] was heated for ten minutes at 230–245° and then distilled at 9 mm. pressure. Crystallization of the distillate from benzene–petroleum ether (60–70°) gave 0.20 g. of m.p. 90.5–91°. Several recrystallizations from acetone–water and acetone–benzene gave an analytical sample, m.p. 90.5–91.5°. *Anal.* Calcd. for $C_{18}H_{14}O_2$: C, 82.5; H, 5.38. Found: C, 82.99, 83.22; H, 5.27, 5.31.

***p*-Methoxyphenyl α-Naphthyl Ketone (III); Proof of Structure of 1-(*p*-Anisoyl)-2-naphthoic Acid (II).**—The reaction of the Grignard reagent from *p*-bromoanisole with α-naphthonitrile gave a 44% yield of crude ketone; after one crystallization, the yield of III was 32%, m.p. 78–80°. Crystallization from a variety of solvents eventually raised the melting point to 81–82°; the substance was identical with that obtained as follows: A mixture of 0.50 g. of the isomer II described above, together with a small amount of its cupric salt, was heated at 230–245° for ten minutes and distilled *in vacuo* (water-pump). The yield was 185 mg. of crude crystalline product. Crystallization from a variety of solvents gave an analytical sample of constant melting point, 81.0–82.0°. *Anal.* Calcd. for $C_{18}H_{14}O_2$: C, 82.5; H, 5.38; CH_3O, 11.8. Found: C, 81.94, 82.14; H, 5.39, 5.46; CH_3O, 12.18, 12.32.

2-[α-Hydroxy-α-(4-methoxyphenyl)-ethyl]-1-naphthoic Acid Lactone (IV).—To a stirred mixture of 20 g. (0.065 mole) of the keto acid I, 250 ml. of dry ether and 450 ml. of dry benzene was added dropwise 154 ml. of 1.25 *M* methylmagnesium bromide (0.192 mole); stirring was continued for four hours at about 40° and overnight at room temperature. Decomposition was accomplished with saturated ammonium chloride solution; ice and hydrochloric acid were added, and the organic layer was separated and washed successively with three portions of cold *N* sodium carbonate and with saturated sodium chloride solution (4.3 g. of I was recovered from the basic extracts). The solution was concentrated, and the residue crystallized from ethanol, yield 14.9 g. (75%; based on unrecovered I, 95.5%), m.p. 128.5–130.5°. A previously obtained sample, m.p. 130.0–131.0° was analyzed. *Anal.* Calcd. for $C_{20}H_{16}O_3$: C, 78.9; H, 5.30. Found: C, 79.70, 79.47; H, 5.29, 5.55.

2-[α-(4-Methoxyphenyl)-ethyl]-1-naphthoic Acid (V).—A mixture of 15.8 g. (0.052 mole) of the lactone IV, 400 ml. of ethanol and 43 ml. of 40% (by weight) sodium hydroxide was refluxed for 20 hours whereupon 315 ml. of solvent was distilled and replaced with water. An additional 35 ml. of solvent was distilled and 50 g. of zinc dust activated with copper sulfate was added, followed by 86 ml. of 40% sodium hydroxide and 35 ml. of water. The mixture was refluxed for 24 hours, cooled, filtered and the zinc residue washed well with hot water. The combined filtrates were made strongly acid and the crystallized mass filtered. The product was reprecipitated from its sodium salt in aqueous acetone by slow addition of dilute acid to give 15.2 g. (95%), m.p. 167.5–169.5°. A previously obtained sample, m.p. 168.5–169.2°, was analyzed. *Anal.* Calcd. for $C_{20}H_{18}O_3$: C, 78.4; H, 5.9. Found: C, 78.66, 78.58; H, 6.11, 6.07.

9,10-Dimethyl-7-methoxy-1,2-benzanthracene (VI).—To 12.8 g. of the acid V in a polyethylene bottle was added about 100 ml. of anhydrous hydrofluoric acid. The solution was swirled occasionally over a period of 20 minutes and poured on cracked ice with stirring. The aqueous supernatant was drawn off through a fritted disk and the product was washed well in this way with ice-water. The anthrone so obtained was taken up in 200 ml. of benzene and the remaining water was separated. The solution was dried with a little anhydrous magnesium sulfate and filtered directly into a stirred solution of 134 ml. of 1.25 *M* methylmagnesium bromide in ether. The mixture was stirred at 40–50° for 1.5 hours and decomposed with saturated ammonium chloride. Ice and hydrochloric acid were added, the mixture was shaken and the clear organic layer separated, concentrated, and the residue heated in a Wood metal-bath up to about 185° until water evolution had practically stopped (about three minutes). Chromatography (adsorbent, 5:1 alumina:Celite by weight; eluent, 2% 60–70° petroleum ether in benzene) gave 6.50 g. (54%) of product, m.p. 137–138.5°. A previously obtained sample, m.p. 136.0–137.0°, was analyzed. *Anal.* Calcd. for $C_{21}H_{18}O$: C, 88.1; H, 6.30; CH_3O, 10.83. Found: C, 88.06, 87.94; H, 6.37, 6.26; CH_3O, 10.79, 10.81.

9,10-Dimethyl-1,2-benzanthryl 7-Isocyanate (VII).—To a flask, with a sidearm through which nitrogen was bubbled, were added 20 ml. of dioxane, 50 mg. of hydroquinone, 1.0 g. of 7-methoxy-9,10-dimethyl-1,2-benzanthracene (VI) and 5 ml. of freshly distilled constant-boiling hydrobromic acid. The mixture was heated on the steam-cone (reflux) for 2.5 hours and then in a metal-bath at 150° while 21 ml. of distillate was removed. The residue was cooled under nitrogen, the aqueous layer was decanted and the reddish oil washed with a little water. It was dissolved in 14 ml. of dioxane and added to a mixture of 5 g. of sodium bisulfite and 8 ml. of water. After addition of 20 ml. of concentrated ammonium hydroxide, the mixture (in the glass liner of an Aminco super-pressure outfit) was rocked at 180–190° for 30 hours and cooled while the apparatus continued to rock; the contents were washed into a low actinic separatory funnel with distilled water and peroxide-free ether. The ether layer was washed with water, dried with saturated sodium chloride and with anhydrous magnesium sulfate, and the ether replaced with benzene by distillation. The

solution was adsorbed on a 3.8 × 19 cm. column containing about 120 g. of 6:1 silicic acid:Celite and eluted with 9:1 benzene:60–70° petroleum ether (purified). The first band (blue fluorescence) was mainly starting methoxy compound (500 mg.; several purifications gave 200 mg. of pure methoxy compound). The eluent was then changed to 30:1 benzene:60–70° petroleum ether and the amine band (greenish fluorescence) passed through. After concentration to about 30 ml. this fraction was added to a stirred solution of about 7 g. of phosgene in 50 ml. of cold dry toluene. The suspension was refluxed until clear (excess phosgene was trapped with Dry Ice and destroyed with alcohol in a good hood) and then concentrated to about 5 ml. Addition of 60–70° petroleum ether to turbidity and several hours of cooling gave 266 mg. of crude isocyanate; sublimation at 115–120° at 0.1 μ gave 179 mg. (17.2%) of isocyanate melting at 113.5–114.5° with softening at 111°; a sample purified for analysis by resublimation melted at 113.8–114.6° with softening at 109°. *Anal.* Calcd. for $C_{21}H_{15}NO$: C, 84.8; H, 5.08; N, 4.71. Found: C, 84.75, 84.63; H, 5.37, 5.25; N, 4.72, 4.69.

7-Amino-9,10-dimethyl-1,2-benzanthracene.—It was possible to crystallize this sensitive compound in low yield from the above hydrocarbon eluent, m.p. 107.5–108.5°. *Anal.* Calcd. for $C_{20}H_{17}N$: N, 5.16. Found: N, 5.23, 5.28. This material (20 mg.) reacted with phosgene to give VII in 50% yield.

ε-(9,10-Dimethyl-1,2-benzanthryl-7-carbamido)-caproic Acid.—To a stirred solution of 262 mg. (2 millimoles) of ε-aminocaproic acid in 15 ml. of water containing 2.1 millimoles of sodium hydroxide and 15 ml. of dioxane was added dropwise a solution of 70 mg. of twice-sublimed 9,10-dimethyl-1,2-benzanthryl 7-isocyanate (VII) in 30 ml. of dioxane. After ten minutes of stirring, acidification, and dilution to about 200 ml., the product was filtered and dried (119 mg.). Precipitation from a solution of the sodium salt in a relatively large volume of 40% ethanol gave 70.5 mg. (69%) of acid which had an $E^{1\%}_{1\,cm.}$ at 372.5 mμ of 162. After exhaustive reprecipitation of the acid from solutions of its sodium salt in 50 and 70% ethanol, material having a constant $E^{1\%}_{1\,cm.}$ of 209 at 372.5 mμ was obtained (sodium salt in 15% ethanol). This material does not keep indefinitely even when refrigerated in the dark as shown by shifts and drop of the absorption curve. Material having a constant absorption curve was analyzed. *Anal.* Calcd. for $C_{27}H_{28}N_2O_3$: N, 6.54. Found: N, 6.48, 6.71.

1-*p*-Methoxybenzyl-2-naphthoic Acid.—To a clear solution of the sodium salt from 15.3 g. (0.05 mole) of the keto acid II in 300 ml. of water were added 40 g. of activated zinc dust and 120 ml. of 40% sodium hydroxide. The mixture was refluxed vigorously for six hours and gently overnight. Another portion of 30 g. of activated zinc dust was added and the mixture was refluxed vigorously for seven hours; a third portion (20 g.) of zinc was added and the mixture refluxed gently overnight, cooled, filtered and the filtrate discarded. The filter cake was leached with hot water until little soluble salt remained; the combined filtrates were acidified and the somewhat oily precipitate was separated from the supernatant by decantation, and taken up in 100 ml. of methanol. The solution was neutralized to phenolphthalein, diluted to 300 ml., and filtered. After addition of 25 ml. of *N* sulfuric acid and 100 ml. of benzene, the organic layer was separated, diluted with 30–60° petroleum ether and cooled. The crystallized product weighed 4.7 g., and had a melting range of 135–162°. It was purified by dissolving in methanol, filtering and diluting with water; the product, m.p. 171–172.5°, weighed 2.2 g. (15%), and had a neutral equivalent of 296. An analytical sample melting at 172–172.9° was prepared. *Anal.* Calcd. for $C_{19}H_{16}O_3$: C, 78.1; H, 5.52. Found: C, 78.09, 78.31; H, 5.84, 5.72.

Upon addition of a second 25-ml. portion of *N* sulfuric acid to the original methanol–water solution, there was obtained 6.1 g. of crystalline material, which on recrystallization from benzene gave 3.8 g. of a compound melting at 143–150° dec. and having a neutral equivalent of 313. Crystallization to constant melting point of 152–153.5° with some gas evolution gave a compound of neut. equiv. 313; the compound once melted would not resolidify on recooling. Evaporation of an acetone solution in the presence of a small amount of acid gave a lactone; the initial presumption that the compound was simply the carbinol intermediate between the starting ketone and the product containing the methylene group was not borne out by the analysis, which in fact corresponds fairly closely to the tetrahydrocarbinol. *Anal.* Calcd. for $C_{19}H_{16}O_4$: C, 74.1; H, 5.24. Found: C, 72.72, 72.79; H, 6.40, 6.38. Calcd. for $C_{19}H_{20}O_4$: C, 73.15; H, 6.45. The compound is indifferent to the further reducing action of zinc and alkali and does not give the starting keto acid on permanganate oxidation.

6-Methoxy-10-methyl-1,2-benzanthracene.—1-*p*-Methoxybenzyl-2-naphthoic acid was cyclized with hydrogen fluoride, allowed to react with four equivalents of methyl Grignard, heated to aromatize the molecule and isolated in the same manner as described for the synthesis of 7-methoxy-9,10-dimethyl-1,2-benzanthracene. The yield from 1.46 g. (0.005 mole) of acid was 0.250 g. (18.4%), m.p. 173.5–175.0°. Sublimation gave an analytical sample of m.p. 174.1–175.1°. *Anal.* Calcd. for $C_{20}H_{16}O$: C, 88.4; H, 5.94; CH_3O, 11.4. Found: C, 88.44, 88.27; H, 6.09, 5.98; CH_3O, 11.40, 11.21.

10-Methyl-1,2-benzanthryl 6-Isocyanate.—This compound was prepared from 170 mg. of 6-methoxy-10-methyl-1,2-benzanthracene under the same experimental conditions used for 9,10-dimethyl-1,2-benzanthryl 7-isocyanate. The amounts of other reagents used were the same as for one gram of the 7-methoxy compound until the reaction with phosgene of the material eluted from the column of silicic acid, where the amine in 10 ml. of benzene was added to a solution of 5 g. of phosgene in 20 ml. of toluene. Concentration to about 1 ml. and dilution with 60–70° petroleum ether gave 30 mg. of isocyanate, m.p. 134–135°, s. 130°. After crystallization from benzene–petroleum ether, 22 mg. (12.5%) of product, m.p. 134.5–135.5°, s. 130°, was obtained for analysis. *Anal.* Calcd. for $C_{20}H_{13}NO$: C, 84.9; H, 4.63; N, 4.95. Found: C, 84.64, 84.89; H, 4.94, 5.16; N, 4.71, 4.82.

Mixture of 2-Benzoyl-7-methoxy-1-naphthoic Acid and 1-Benzoyl-7-methoxy-2-naphthoic Acid.—The Grignard reagent, in 300 ml. of dry ether, was prepared from 4.5 g. of magnesium and 18.9 ml. (0.18 mole) of bromobenzene and added to a stirred solution of 37.6 g. (0.165 mole) of 7-methoxy-1,2-naphthalic anhydride in about 700 ml. of benzene. After addition of two-thirds in a slow stream, the remainder of the Grignard solution was added dropwise. The mixture was stirred at about 45° for an hour; then it was poured on ice and hydrochloric acid. When decomposition was complete, the layers were separated, acetone was added to the organic layer to keep the product in solution and two benzene–ether extracts of the aqueous layer were added to it. After washing with water, the combined organic extracts were extracted several times with portions of 0.5 *N* sodium hydroxide totaling 700 ml. After treatment of the basic solution with decolorizing carbon, 100 ml. of acetone was added, followed by the dropwise addition, with stirring, of *N* sulfuric acid (150 ml. after crystallization commenced). The mixed acids showed a neutral equivalent of 319 (theory 306) and weighed 34.4 g. (68.2%). Another precipitation of the acid from a solution of the salt in water–acetone gave 32 g., neut. equiv. 304, m.p. 169–181°. One of the isomers, presumably the 2-benzoyl-1-naphthoic acid, m.p. 203.5–204.5°, was later isolated and used as noted below.

2-(α-Hydroxy-α-phenylethyl)-7-methoxy-1-naphthoic Acid Lactone.—To a stirred suspension of 23.7 g. (0.13 mole) of the keto acid mixture in 300 ml. of dry ether and 550 ml. of dry benzene was added rapidly 105 ml. of 1.25 *M* methylmagnesium bromide, followed by the dropwise addition of an additional 81 ml. After stirring at about 40–45° for two hours and at about 30° overnight, the mixture was decomposed with ice and hydrochloric acid. The organic layer was separated, extracted several times with cold *N* sodium carbonate, dried with saturated sodium chloride solution and with anhydrous magnesium sulfate, filtered and concentrated on the steam-cone. Most of the remaining benzene was entrained in a stream of nitrogen; 15 ml. of ethanol and 20 ml. of 60–70° petroleum ether were added. The product was removed by filtration, yield 11.9 g., m.p. 137–139°. The yield was 50.5% based on keto acid taken, or allowing for 6.0 g. recovered from the sodium carbonate extracts, 67.7%. A previously obtained sample of melting point 138.0–138.6° was analyzed. *Anal.* Calcd. for $C_{20}H_{16}O_3$: C, 78.9; H, 5.30. Found: C, 79.04, 79.16; H, 4.84, 4.94. The same material was obtained in 92.5% yield from the pure isomer of m.p. 203.5–204.5° noted above.

7-Methoxy-2-(α-phenylethyl)-1-naphthoic Acid.—The lactone was hydrolyzed and reduced with activated zinc dust and alkali in the same way as described for IV. The yield from 13.4 g. of lactone was 13.1 g. (97%), m.p. 153–154.5°. An analytical sample prepared by vacuum sublimation melted at 155–155.5°. *Anal.* Calcd. for $C_{20}H_{18}O_3$: C, 78.4; H, 5.9. Found: C, 78.42, 78.49; H, 5.76, 5.81.

2'-Methoxy-9,10-dimethyl-1,2-benzanthracene.—The above naphthoic acid was cyclized with hydrogen fluoride, allowed to react with four equivalents of methyl Grignard, and heated to aromatize the molecule in much the same manner as described for its 7-methoxy isomer. Concentration of the 20:1 benzene:60–70° petroleum ether eluent from the chromatogram gave a first crop of 2.25 g. of product, m.p. 131–132.5°, and a second crop of 0.32 g., m.p. 128.5–130°. The total yield of 2.57 g. of product from 6.1 g. of naphthoic acid amounted to 45.7% of theory. A sample of melting point 131.0–132.5° was analyzed. *Anal.* Calcd. for $C_{21}H_{18}O$: C, 88.1; H, 6.30; CH_3O, 10.83. Found: C, 88.2, 88.1; H, 6.31, 6.45; CH_3O, 10.40, 10.69.

PHILADELPHIA 11, PENNA.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH]

The Conversion of 1,4,6-Tri-*O*-benzoyl-2,3-*O*-(1-benzyloxybenzylidene)-β-D-fructofuranose to 1,4,6-Tri-*O*-benzoyl-2,3-*O*-(1-ethoxybenzylidene)-β-D-fructofuranose by Acidic Ethanol

BY ROBERT K. NESS AND HEWITT G. FLETCHER, JR.

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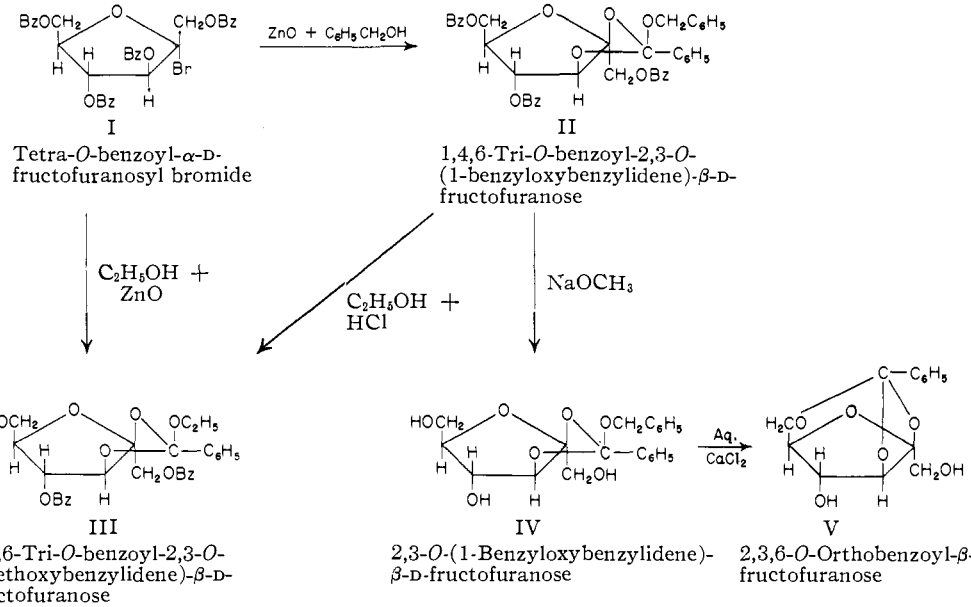
The benzyloxy group in 1,4,6-tri-*O*-benzoyl-2,3-*O*-(1-benzyloxybenzylidene)-β-D-fructofuranose (II) is rapidly replaced by an ethoxy group through treatment with ethanol in the presence of a trace of acid. The product, 1,4,6-tri-*O*-benzoyl-2,3-*O*-(1-ethoxybenzylidene)-β-D-fructofuranose (III), was synthesized through the condensation of tetra-*O*-benzoyl-α-D-fructofuranosyl bromide (I) with ethanol in the presence of zinc oxide.

Helferich and his co-workers[1,2] have recently reported the condensation of amorphous tetra-*O*-benzoyl-α-D-fructofuranosyl bromide (I) with benzyl alcohol in the presence of zinc oxide as an acid acceptor to obtain a crystalline orthobenzoic acid derivative to which they assigned structure II, 1,4,6-tri-*O*-benzoyl-2,3-*O*-(1-benzyloxybenzylidene)-β-D-fructofuranose. On debenzoylation of this substance, they obtained 2,3-*O*-(1-benzyloxybenzylidene)-β-D-fructofuranose (IV) as a sirup which, under the action of aqueous calcium chloride, lost a molecule of benzyl alcohol to give a crystalline orthobenzoylfructofuranose; evidence indicated this latter compound to have the 2,3,6-structure V.

A similar transformation in the D-ribopyranose series has more recently been reported by Fletcher and Ness[3] who found that 1,2-*O*-(1-benzyloxybenzylidene)-α-D-ribopyranose (VI) loses benzyl alcohol when treated with very weakly acidic, aqueous acetone to give 1,2,4-*O*-orthobenzoyl-α-D-ribopyranose (VII). These two transformations, IV → V and VI → VII, were *intra*molecular reactions, a free hydroxyl of the sugar itself taking part. However, if the hydroxyl groups were masked as, for instance, in II it is not unreasonable to suppose that an alkoxy group might be induced to replace the benzyloxy residue in an analogous *inter*molecular fashion. This has now been found to take place.



I Tetra-*O*-benzoyl-α-D-fructofuranosyl bromide

II 1,4,6-Tri-*O*-benzoyl-2,3-*O*-(1-benzyloxybenzylidene)-β-D-fructofuranose

III 1,4,6-Tri-*O*-benzoyl-2,3-*O*-(1-ethoxybenzylidene)-β-D-fructofuranose

IV 2,3-*O*-(1-Benzyloxybenzylidene)-β-D-fructofuranose

V 2,3,6-*O*-Orthobenzoyl-β-D-fructofuranose

(1) B. Helferich and L. Bottenbruch, *Chem. Ber.*, **86**, 651 (1953).
(2) B. Helferich and W. Schulte-Hürmann, *ibid.*, **87**, 977 (1954).
(3) H. G. Fletcher, Jr., and R. K. Ness, THIS JOURNAL, **77**, 5337 (1955).