100° oil-bath for seventy-two hours. The product, obtained by precipitation with methyl alcohol, was a white powder. No unreacted acenaphthylene was found. A softening point of approximately 160° was found for this material.

A similar experiment, using vinyl acetate in place of methyl methacrylate, was also carried out. This copolymerization product of (II) with vinyl acetate had a softening point of about 180°.

All of the polymerization and copolymerization products of (II) were found to be soluble in benzene and trichloroethylene, and insoluble in methyl alcohol, acetone and ether.

**Acknowledgment.**—The authors wish to thank Dr. Kenneth Goldblum of the General Electric Plastics Laboratory, for the molecular weight measurements.

## Summary

Two improved methods for the preparation of acenaphthylene have been described. A high molecular weight polymer of acenaphthylene and polymerization products of acenaphthylene with vinylcarbazole, styrene, methyl methacrylate and vinyl acetate, were prepared.

Received February 8, 1947

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[Contribution from the Radiation Laboratory and Chemistry Department of the University of California]

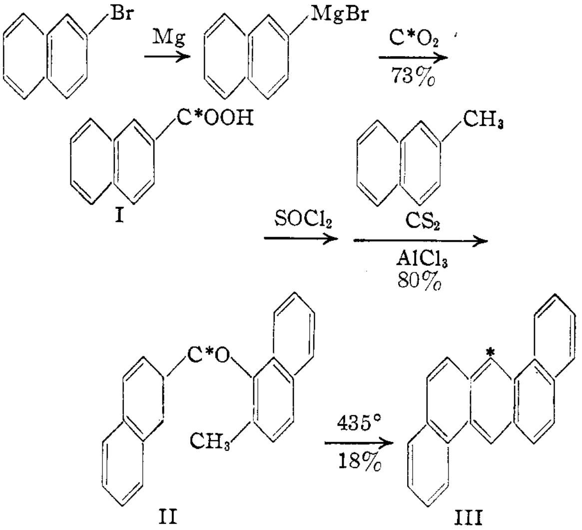
# The Synthesis of 1,2,5,6-Dibenzanthracene Labeled in the 9-Position with Carbon-14[1]

By Charles Heidelberger, Phyllis Brewer and William G. Dauben

Ever since the discovery of the carcinogenic power of certain pure polynuclear aromatic hydrocarbons by Kennaway and Hieger[2] in 1930, these substances have been the subject of a considerable number of investigations of the relationship of structure and carcinogenic power. This work was carried on chiefly by Cook and his co-workers in England and by Fieser and his group in America and has resulted in the assay of over a thousand compounds for their ability to produce tumors in mice. The three highly active compounds that have been most widely studied are 20-methylcholanthrene, 3,4-benzpyrene, and 1,2,5,6-dibenzanthracene. Recent studies of the metabolism of dibenzanthracene by R. N. Jones,[3] utilizing ultraviolet absorption as his analytical technique, have given considerable insight into the distribution of this compound in the animal organism. There still remains the question of studying the degradation and other chemical transformations of the carcinogenic hydrocarbons, and long-lived radioactive carbon appeared to offer a method by which these and similar problems may be investigated. Therefore, we have synthesized 1,2,5,6-dibenzanthracene labeled in the 9-position.

The preparation of this compound was carried out according to the procedure of Fieser and Cason.[4] The acid chloride, prepared from $\beta$-naphthoic acid, was allowed to react with $\beta$-methylnaphthalene and aluminum chloride. The resulting ketone was pyrolyzed at 435°, and dibenzanthracene was obtained. The $\beta$-naphthoic acid was prepared by carbonation of the Grignard reagent from $\beta$-bromonaphthalene with radioactive carbon dioxide according to the method of Dauben, Reid and Yankwich.[5]

The following is a summary of the reactions employed and the yields obtained[6]



The over-all yield of dibenzanthracene based on carbon dioxide was 11%.

A number of trial runs using non-isotopic carbon dioxide were carried out on the scale employed in the final synthesis, and the over-all yields based on carbon dioxide ranged from 6–12%. The yield in the carbonation reaction was lower than those reported by Dauben, Reid and Yankwich[5] for several other acids, owing to the formation of a considerable neutral fraction from which some dinaphthyl ketone could be isolated. The Friedel and Crafts reaction ran smoothly on a small scale,

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[1] This paper is based on work performed under Contract W-7405-Eng-48 with the Manhattan Project in connection with the Radiation Laboratory and the Department of Chemistry of the University of California.

[2] Kennaway and Hieger, *British Med. J.*, **1**, 1044 (1930).

[3] Jones, Dunlap and Gogek, *Cancer Research*, **4**, 209 (1944), and earlier papers.

[4] Fieser, "Organic Reactions," Vol. I, John Wiley and Sons, N. Y., 1942, p. 151.

[5] Dauben, Reid and Yankwich, in preparation.

[6] The radioactive carbon atom is indicated by an asterisk. It must be remembered that although only one carbon is labeled, owing to the symmetry of the molecule the compound will react as though both of the *meso* positions are marked.

and the oily ketone was obtained by vacuum distillation.

A study of the Elbs reaction was carried out, in which the ketone was pyrolyzed for varying lengths of time. A relatively large amount of yellow product was obtained after the ketone was heated for forty-five minutes, but this mixture could not be decolorized by two treatments with lead tetraacetate, which sufficed, however, to decolorize the product obtained by heating the ketone for ninety minutes. The highest yield of colorless dibenzanthracene was obtained when the reaction was heated for three and one-half hours, and only one treatment with lead tetraacetate was required for the purification.

The effluent gas from the pyrolysis of the material was swept with nitrogen directly into a combustion furnace, the carbon dioxide was precipitated with barium carbonate and was found to be highly radioactive. This observation indicates that some of the extensive decomposition that occurs during the Elbs reaction involves volatilization of the carbonyl carbon atom. The residues from all the reactions were combined and burned in a macro combustion furnace, and the resulting radioactive barium carbonate contained 36% of the original activity. Hence, including the product, 40% of the original radioactivity was recovered. The purified colorless dibenzanthracene has a specific activity of 67,000 cts./min./mg. D.B.A., (0.385 microcurie/mg.) and biological investigations with this substance are now under way in these laboratories.

**Acknowledgments.**—We are indebted to Professor Melvin Calvin and Dr. Peter Yankwich for their interest and help in this work.

## Experimental[6a]

**Carboxyl-labeled β-Naphthoic Acid. I.**—The Grignard reagent was prepared in an all-glass apparatus under nitrogen from 0.48 g. (0.02 mole) of magnesium turnings and 4.14 g. (0.02 mole) of β-bromonaphthalene dissolved in 16 cc. of dry ether and 4 cc. of dry benzene. The reaction started when the mixture was heated, and refluxing was continued for one hour. The dark mixture was cooled, an aliquot titrated, and the solution was found to contain 0.00119 mole of Grignard reagent per cc.

A volume of 8.1 cc. of Grignard solution (0.00966 mole) was transferred, using a hypodermic syringe, to a three-necked flask attached to the vacuum line and fitted with an internal induction stirrer. The flask was swept with a vigorous stream of nitrogen during the transfer, and 10 cc. of a 2:1 mixture of anhydrous ether and benzene was added. The reaction flask was closed, cooled in liquid nitrogen, and evacuated to $5 \times 10^{-4}$ mm. The system was isolated from the vacuum pump by means of a stopcock and was warmed to −20° (ice–acetone bath) to allow nitrogen entrapped by freezing of the Grignard reagent solution to escape, and the flask was again frozen in liquid nitrogen and re-evacuated to $5 \times 10^{-4}$ mm. The system was then isolated, and the reaction vessel was warmed to −20° at which temperature the carbonation was carried out with vigorous stirring.

A sample of barium carbonate had previously been prepared, which weighed 1.586 g. (0.008053 mole) with specific activity[7] of 94,500 cts./min./mg. of barium carbonate. The radioactive barium carbonate was placed in a 50-ml. Erlenmeyer flask fitted with a ground joint and connected to a small pressure equalizing dropping funnel containing 15 ml. of concentrated sulfuric acid. The dropping funnel was in turn attached to the vacuum line by means of a tube containing Drierite.

When the solution of Grignard reagent had reached equilibrium at −20°, the entire system contained ether vapor at a pressure of 78 mm. Carbon dioxide was then generated by addition of sulfuric acid to the barium carbonate. The uptake of carbon dioxide is rapid with efficient stirring, and the sulfuric acid was dropped in at such a rate that the pressure in the system never exceeded 100 mm. After twenty minutes the uptake was complete (manometer, 78 mm.), and the gas generation flask was gently warmed to drive off all traces of carbon dioxide. The reaction vessel was then frozen in liquid nitrogen, warmed to −20° and frozen again; the flask was closed off from the rest of the vacuum line, and the contents were stirred at 0° for fifteen minutes. Air was admitted to the system, and the reaction mixture was hydrolyzed with ice and dilute hydrochloric acid. The flask was rinsed with ether, the layers were separated, and the ethereal layer was washed with water and extracted six times with 5% sodium bicarbonate. The neutral fraction was saved for combustion to recover radioactive carbon. The aqueous phase was carefully acidified, the β-naphthoic acid came out as a colorless precipitate and was extracted with ether. The ethereal solution was extracted twice with 10% sodium hydroxide, and the ether was combined with the neutral fraction. On acidification of the aqueous layer, a crystalline precipitate of β-naphthoic acid was obtained, which on filtration and drying gave a yield of 1.00 g., m. p. 81–183.5°, 73% based on carbon dioxide. Specific activity[8] × 11: 93,800 cts./min./mg. barium carbonate.

**Carbonyl-labeled 1-(2-Naphthoyl)-2-methylnaphthalene II.**—To a suspension of 0.95 g. of labeled β-naphthoic acid in 8 cc. of dry benzene was added 2 cc. of purified thionyl chloride, and the mixture was refluxed for one hour, after which the excess thionyl chloride and benzene were distilled in vacuum. A mechanical stirrer was attached to the flask containing the dark crystalline acid chloride, and a solution of 0.95 g. of redistilled β-methylnaphthalene in 4 cc. of carbon disulfide was added. Anhydrous aluminum chloride (0.95 g.) was added over a period of fifteen minutes, and the dark mixture was refluxed for one hour. The hydrolysis was accomplished with dilute hydrochloric acid, and the carbon disulfide was removed by steam distillation. The ketone was extracted with benzene, washed with water, and distilled. A yield of 1.30 g. (80%) of yellowish viscous oil was obtained, b. p. 212–215° (0.5 mm.). The evaporated aqueous washings and the distillation residue were burned for recovery of radioactive carbon.

**9-Labeled 1,2,5,6-Dibenzanthracene III.**—The Elbs pyrolysis was run in a small distillation flask with a sealed-on receiver, heated in a salt-bath thermostatically controlled at 435°. The ketone (1.25 g.) was pyrolyzed for three and one-half hours, the gases evolved were passed directly into a combustion furnace, and the entire system was swept with nitrogen. A precipitate of 0.3304 g. of highly radioactive barium carbonate was collected from the combustion.

When the reaction was complete, glass wool was added, the top of the flask was sealed, and the dibenzanthracene

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[6a] All melting points are corrected. Microcombustions by Mrs. W. B. Dandliker and Mr. C. F. Koch.

[7] All measurements of radioactivity were carried out on a thin mica-window Geiger–Müller tube on a scale of 64 circuit with a geometry of 12.9 disintegrations per count. The activity was determined with thin uniform layers of barium carbonate according to the procedure of Dauben, Reid and Yankwich,[5] and Yankwich, Norris and Houston (paper in preparation). Over-all counting error was ±2%.

[8] This value was obtained by combustion of a micro sample with benzoic acid as a carrier, precipitation of carbon dioxide as barium carbonate, which was counted. To correct for the dilution of activity in the compound, the observed specific activity is multiplied by eleven.

was distilled at 1 mm., bath temperature 350–400°. The residue was burned to recover radioactive carbon. The yellow distillate was dissolved in hot benzene and was crystallized to give 0.330 g. of yellow dibenzanthracene, m. p. 231–243°. The purification was accomplished by boiling for one hour a mixture of 0.330 g. of yellow dibenzanthracene and 0.07 g. of lead tetraacetate in 16 cc. of benzene and 16 cc. of acetic acid. The reaction mixture was concentrated to a volume of 12 cc. The colorless dibenzanthracene was removed by filtration and washed with cold acetic acid: yield 0.230 g.; m. p. 249–253°. The product was recrystallized from benzene to give pure colorless plates of dibenzanthracene: yield 0.207 g.; m. p. 259–262°. Thus the over-all yield of pure dibenzanthracene, based on barium carbonate, is 11%.

*Anal.* Calcd. for $C_{22}H_{14}$: C, 94.93; H, 5.07. Found: C, 94.55; H, 5.48. Specific activity × 22, 94,000 counts/min./mg. barium carbonate. Activity of compound: 67,000 cts./min./mg. D. B. A.

**Practice Elbs Reactions.**—A. Pyrolysis time, 45 minutes; wt. ketone, 2.20 g.; wt. crude yellow compound, 0.78 g., m. p. 231–246°. Remained yellow after two treatments with 0.15 g. of lead tetraacetate.

**B.** Pyrolysis time, one and one-half hours; wt. ketone, 2.20 g.; wt. crude yellow compound, 0.65 g., m. p. 221–231°. Required two treatments, 0.26 g. of lead tetraacetate; wt. colorless compound, 0.36 g., m. p. 245–255°.

**C.** Pyrolysis time, three and one-half hours; wt. ketone, 2.20 g.; wt. crude yellow compound, 0.60 g., m. p. 246–261°. Required only one treatment with lead tetraacetate 0.12 g. Wt. colorless compound 0.46 g., m. p. 259–261°.

**Determination of Specific Activities.**—A typical determination was carried out as follows: A sample of 1.184 mg. of radioactive β-naphthoic acid was weighed into one boat, and 31.608 mg. of inactive benzoic acid was placed in another. The boats were inserted in a micro combustion furnace connected to a sodium hydroxide bubbler. The naphthoic acid was burned first, and then the benzoic acid. The carbon dioxide was precipitated as barium carbonate, and 378.2 mg. was obtained from which plates were made, with specific activities of 336, 336 and 338 cts./min./mg. barium carbonate.

$$\text{Specific activity} \times 11 = \frac{337 \times 378.2 \times 11}{1.184 \times 16.4 \times .77} = 93{,}800\ \text{cts./min./mg.}$$

barium carbonate, where 16.4 is the molecular weight ratio of barium carbonate/carbon and 0.77 is the fraction of carbon in naphthoic acid.

**Combustion of Residues.**—From the combustion of the combined residues, 22.9 g. of barium carbonate was recovered. For the determination of specific activity a 19.004-mg. sample was diluted with inactive carbonate to a weight of 332.9 mg. of barium carbonate from which three plates were obtained with specific activities of 130, 134 and 137 cts./min./mg. barium carbonate. Specific activity of sample from combustion = 134 × 332.9/19.004 = 2345 cts./min./mg. barium carbonate.

## Summary

1. 1,2,5,6-Dibenzanthracene, labeled with carbon fourteen in the 9-position has been synthesized in 11% over-all yield based on carbon dioxide.

2. A study of the Elbs reaction of 1-(2-naphthoyl)-2-methylnaphthalene has shown that the volatile by-products largely result from the carbonyl carbon and that optimum yields are obtained when the reaction is heated for three hours or more.

BERKELEY, CALIFORNIA RECEIVED FEBRUARY 24, 1947

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[CONTRIBUTION FROM RESEARCH LABORATORIES OF THE J. T. BAKER CHEMICAL COMPANY]

# Tartaric, *o*-Sulfobenzoic and β-Sulfopropionic Acid Derivatives of Some Sulfonamides

BY V. B. FISH, J. R. STEVENS AND R. G. D. MOORE

A number of polycarboxylic acid derivatives of some of the sulfonamides has been reported by Moore and Miller.[1] These compounds were prepared by one or more of three general methods. These general methods include the condensation of the desired sulfonamide with an acid anhydride, ester or the free acid. In a patent, Moore,[2] mentioned 2-N$^4$-tartarylsulfanilamidothiazole, but did not describe the properties of the compound or specific conditions for its preparation.

No mention has been found in the literature of the preparation of N$^4$-sulfocarboxylic acid derivatives of the sulfonamides. It seemed desirable to prepare such compounds for pharmacological evaluation.

The 2-N$^4$-tartaryl and diacetyltartaryl derivatives (I) were prepared by the action of diacetyltartaric anhydride[3] on a solution or suspension of the sulfonamide in glacial acetic acid or anhydrous pyridine. In general, the reaction mixtures were heated to about 80° for two hours. The crude products either crystallized on cooling or were precipitated by pouring the reaction mixture into benzene when acetic acid was used as a reaction medium. When the reaction was made in pyridine the subsequent treatment was varied to suit the particular case. The crude products were recrystallized from a suitable solvent until a satisfactory product was obtained. The tartaryl derivatives were prepared from the corresponding diacetyl compounds by a mild alkaline hydrolysis.

$$HO_2C\overset{(Ac)}{C}HOH\overset{(Ac)}{C}HOHCONHC_6H_4SO_2NHY \quad (I)$$

The derivatives of *o*-sulfobenzoic acid (II) were prepared by the action of *o*-sulfobenzoic anhydride on the sulfonamide in anhydrous pyridine. The pyridine salts were isolated and purified by recrystallization from water or aqueous alcohol. The pyridine salts were converted to the corresponding sodium salts by treatment with a

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[1] Moore and Miller, THIS JOURNAL, **64**, 1572 (1942).

[2] Moore, U. S. Patent 2,324,013 (1943).

[3] Wohl and Oesterlin, *Ber.*, **34**, 1144 (1901).