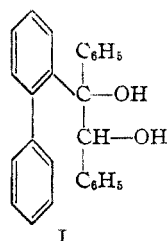


[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF DUKE UNIVERSITY]

Aromatic Cyclodehydration. XV.¹ 9,10-bis-(*p*-Hydroxyphenyl)-phenanthreneBY CHARLES K. BRADSHER² AND LENNARD J. WISSOW

While earlier communications of this series have described the formation of the phenanthrene nucleus through the cyclization of a chlorohydrin,³ an amino alcohol,³ olefin oxides,⁴ and various glycol ethers,^{3,5} we have not hitherto reported the cyclization of a glycol. The present communication deals with two examples of such a cyclization.

Benzoin was treated with over two moles of 2-biphenylmagnesium iodide to give a product which apparently was a mixture of diastereoisomeric glycols (I). This mixture was cyclized

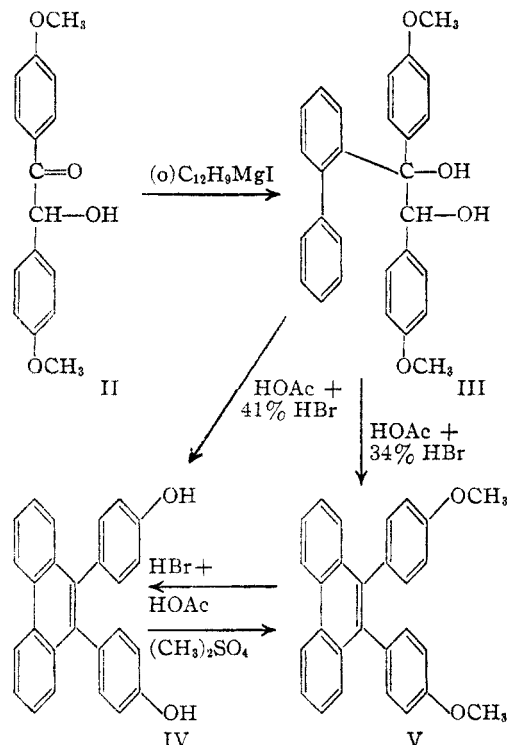


directly to yield 9,10-diphenylphenanthrene in an over-all yield of 29% (calculated from the benzoin).

It is obvious that the preparative value of this synthesis is limited by the necessity for the wasteful destruction of one mole of biphenylmagnesium iodide for every mole of the benzoin. This handicap may be eliminated by conversion of the benzoin to an ether,⁶ but it was felt that in the case of a more difficultly prepared benzoin, the more direct route might be used advantageously.

In the single such case studied, our efforts met with some success. Anisoin (II) was treated with 2-biphenylmagnesium iodide and the resulting carbinol⁷ (III) cyclized by a mixture of acetic and 41% hydrobromic acids. The expected 9,10-bis-(*p*-hydroxyphenyl)-phenanthrene (IV) was obtained in 28% yield. Although this compound gave erratic results when analyzed for carbon and hydrogen, the three derivatives had the expected composition.

In a single run in which 34% hydrobromic acid was used, the only product isolated was 9,10-bis-(*p*-methoxyphenyl)-phenanthrene (V). The identity of the ether was demonstrated both by demethylation to yield the diphenol (IV) and by its preparation from the latter by the action of methyl sulfate. The fact that demethylation can be accomplished by the use of a mixture of hydro-



bromic and acetic acids suggests that this ether is an intermediate in the preparation of the diphenol (IV).

Experimental

1-(2-Biphenyl)-1,2-diphenylglycol (I).—A Grignard reagent was prepared from 30.8 g. of *o*-iodobiphenyl and a solution containing 10.6 g. of dry benzoin in dry benzene was added. The reaction mixture was refluxed for six hours, after which it was decomposed by ice and hydrochloric acid. The solvent layer was separated, washed, concentrated and the residue used in the following experiment.

9,10-Diphenylphenanthrene.—The impure glycol obtained above was refluxed for two days in a mixture containing 100 cc. of 48% hydrobromic and 100 cc. of acetic acids. The product which crystallized from the reaction mixture was recrystallized from acetic acid as white needles, m. p. 234–235°; yield 3.9 g. (29%, based on the benzoin). The identity of the product was established by a mixed melting point determination with an authentic sample of 9,10-diphenylphenanthrene.⁶

1,2-bis-(*p*-Methoxyphenyl)-1-(2-biphenyl)-glycol (III) was prepared from 27.2 g. of anisoin (II) in a manner analogous to that employed in the preparation of the diphenylglycol (I). The crude product was used directly in the following reaction.

9,10-bis-(*p*-Hydroxyphenyl)-phenanthrene (IV).—The crude glycol (III) was refluxed for forty-eight hours with 100 cc. of acetic acid and 150 cc. of 48% hydrobromic acid. The product was collected and recrystallized from acetic acid or ethyl alcohol as a white microcrystalline solid, m. p. 296–298° (shrinks at 286–288°); yield 10 g. (28%).

The product was soluble in sodium hydroxide solution. It gave erratic results when analyzed for carbon and

(1) For the preceding communication of this series, see *THIS JOURNAL*, **65**, 2016 (1943).

(2) National Research Fellow (participating basis, 1941–1942).

(3) Bradsher and Tess, *THIS JOURNAL*, **61**, 2184 (1939).

(4) E. g., Bradsher, *ibid.*, **61**, 3131 (1939).

(5) Bradsher and Schneider, *ibid.*, **60**, 2980 (1938).

(6) Bradsher and Rosher, *ibid.*, **61**, 1524 (1939).

(7) Probably a mixture of diastereoisomers.

hydrogen, but its derivatives all had the expected composition.

The diacetate was prepared by refluxing the diphenol with acetic anhydride in pyridine. The product was obtained as white plates from acetic acid, m. p. 234°.

*Anal.*⁸ Calcd. for $C_{30}H_{22}O_4$: C, 80.72; H, 4.93. Found: C, 80.79; H, 4.79.

The dipropionate was prepared by refluxing the diphenol for two hours with propionyl chloride. The hot mixture was poured on ice, the product collected and recrystallized from acetic acid as fine plate-like white crystals, m. p. 185–186°.

Anal. Calcd. for $C_{32}H_{26}O_4$: C, 81.01; H, 5.48. Found: C, 80.81; H, 5.79.

The dipropionate was saponified by refluxing with 10% alcoholic potassium hydroxide solution which, upon acidification, gave the diphenol, m. p. 296–298°. This gave no depression of melting point when mixed with the original sample.

9,10-bis-(*p*-Methoxyphenyl)-phenanthrene (V).—(a) By cyclization of the glycol (III): 1,2-bis-(*p*-methoxyphenyl)-1-(2-biphenyl)-glycol (III) was prepared from 40.8 g. of anisoin as previously described. This glycol was cyclized as described under the preparation of 9,10-bis-(*p*-hydroxyphenyl)-phenanthrene (IV) except that 34% hydrobromic acid was used instead of the 41% acid. The

product, purified by repeated crystallization from acetic acid, was obtained as a mat of very fine white needles, m. p. 256°; yield 1.3 g. (2%).

(b) From the diphenol: a sample of 9,10-bis-(*p*-hydroxyphenyl)-phenanthrene was dissolved in 10% sodium hydroxide solution and treated with an excess of methyl sulfate. The white solid formed was collected and recrystallized from acetic acid, m. p. 256–258°, and gave no depression of melting point when mixed with a sample prepared from the glycol as described above.

Anal. Calcd. for $C_{28}H_{22}O_2$: C, 86.15; H, 5.64. Found: C, 86.27; H, 5.79.

The dimethyl ether was refluxed for twenty-four hours with a mixture of hydriodic and acetic acids and the product recrystallized from alcohol, m. p. 296–298°. This was shown to be identical with 9,10-bis-(*p*-hydroxyphenyl)-phenanthrene by means of a mixed melting point determination. Essentially the same result was obtained if the ether was refluxed for forty-eight hours with a mixture of acetic and 42% hydrobromic acids.

Summary

By aromatic cyclodehydration of suitable 2-biphenyl glycols, 9,10-diphenyl- and 9,10-bis-(*p*-hydroxyphenyl)-phenanthrene have been prepared.

DURHAM, N. C.

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(8) Analyses by T. S. Ma.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, NORTHWESTERN UNIVERSITY DENTAL SCHOOL]

The Synthesis of Some Alkyl and Dialkylaminoalkyl Esters of 3-Amino-4-fluorobenzoic Acid

By L. S. FOSDICK AND A. F. DODDS^{1a}

In 1941, some alkamine esters of *p*-fluorobenzoic acid were prepared^{1b} and the pharmacological properties studied.² It was found that these compounds produced anesthesia both when injected and when applied topically to mucous membrane. The anesthetic efficiency when injected was equal to or slightly greater than that of procaine hydrochloride. The toxicity of the procaine analog was one-third that of procaine. The toxicity of other members of the series was also very low. All of the compounds produced some tissue irritation, and all of them, with the exception of the procaine analog, produced definite tissue necrosis.

In view of the low toxicities and relatively high anesthetic efficiencies of these compounds, it was thought interesting to continue the investigation. It seemed to us that the introduction of both an amino and a fluoro group on the benzene ring might lower the toxicity. It was hoped that the resultant compounds would not be irritating to tissue. This paper deals with the esters of 3-amino-4-fluorobenzoic acid. The other isomers are in the process of synthesis.

As fluorobenzoic acid was not readily available, it was prepared by oxidizing *p*-fluorotoluene. The *p*-fluorotoluene was prepared by the method of Schiemann³ and was oxidized to *p*-fluorobenzoic acid with potassium permanganate by the method of Slothouwer.⁴ It was then nitrated with fuming nitric acid by the method of Rouche⁵ and converted to the acid chloride by refluxing with thionyl chloride. The fluoro nitro esters were prepared by refluxing the acid chloride with the appropriate alcohol. Finally, the nitro group was reduced with hydrogen, using platinum oxide as the catalyst.

The toxicity of the dialkylaminoalkyl 3-amino-4-fluorobenzoate hydrochlorides was determined by subcutaneous injection in white mice, and the anesthetic efficiency was estimated by the method of Schmitz.⁶ All of the salts were potent topical anesthetics, with the exception of the dimethylaminoethyl ester hydrochloride. A 2% solution of the other members of the series varied from one-half the effectiveness to equal that of a 1% solution of cocaine hydrochloride. The diethylaminoethyl ester hydrochloride was three-fourths as effective as cocaine.

The toxicities of the compounds tested were

(1a) Abstract of a thesis submitted to the faculty of the Graduate School of Northwestern University by A. F. Dodds in partial fulfillment of the requirements of the degree of Doctor of Philosophy.

(1b) Fosdick and Campaigne, *THIS JOURNAL*, **63**, 974 (1941).

(2) Campaigne, Starke, Fosdick and Dragstedt, *J. Pharm. Exptl. Ther.*, **71**, 59 (1941).

(3) Balz and Schiemann, *Ber.*, **60**, 1186 (1927).

(4) Slothouwer, *Rec. trav. chim.*, **33**, 324 (1914).

(5) Rouche, *Bull. Sci. Acad. Roy. Belg.*, **7**, 534 (1921).

(6) Schmitz and Loevenhart, *J. Pharmacol.*, **24**, 159 (1924).