[CONTRIBUTION FROM THE ROSS CHEMICAL LABORATORY, ALABAMA POLYTECHNIC INSTITUTE]

The Chemistry of Phosphonic Acids with Aromatic Nuclei. I. Orientation of Phosphorus in Friedel–Crafts Synthesis

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RECEIVED MARCH 3, 1952

An investigation of the products formed in the Friedel–Crafts reaction between phosphorus trichloride and toluene showed that substantial amounts of the meta isomer, besides lesser amounts of the ortho isomer, are formed in addition to the predominant formation of the para isomer. This finding calls for a re-evaluation of the physical constants of numerous products derived from alkylbenzenes through the initial formation of dichlorophosphines by the Friedel–Crafts method. Indications are that other alkylbenzenes behave analogously to toluene.

When Michaelis and his students[1] reported the application of the Friedel–Crafts method to the preparation of aryldichlorophosphines, they indicated the possibility of formation of more than one isomer in this step. However, they were unable to isolate such isomeric by-products. When alkylbenzenes were used as the starting materials, the para isomers were the only isolated products. In most cases no specific data about the yields were cited; usually proof of structure for the para isomers was given. The establishment of the orientation of phosphorus in these products was very seriously hindered by the inefficiency of the method of isolation of the dichlorophosphines.

The recent development of two satisfactory methods for working-up the reaction mixtures from such Friedel–Crafts reactions now affords an approach to this problem.[2a,2b]

Some time ago the writer suggested that the modern methods of isolation might reveal isomers other than the expected para derivatives from such reactions.[3] This suggestion was based in part on the description of several phosphorus compounds as liquids, instead of the crystalline solids that might have been expected. This has been particularly true of products that had been purified exclusively by distillation procedures.

The possibility of formation of isomer mixtures is mentioned in some of the recent work in this field,[4] but other uncritical work implies that only a single isomer (para) is formed in the Friedel–Crafts reaction with alkylbenzenes.[5]

In the study of this problem we made use of both improved methods of isolation of the reaction products.[2] Neither aryldichlorophosphines, nor dialkyl arylphosphonates could be separated into the individual isomers by distillation. However, when the reaction products were converted to free phosphonic acids, the separation was effected by an extended fractional crystallization. The ratio of the isomers that were isolated from the reaction with toluene was found to be 6.3:2.7:1.0 for para:meta:ortho derivatives, respectively. Since some 15% of the product was not recovered from the fractional crystallization scheme, it may be presumed that the actual proportions of the meta and the ortho isomers, which are most soluble, in the original reaction mixture might have been somewhat higher than indicated above. It is also possible that variations of the conditions of the synthesis may affect the ratio of the isomeric substances formed.

An examination of the reaction with ethylbenzene indicated that the results in this instance are analogous to those found for toluene.

Experimental Part

Toluenephosphonic Acids. a.—Toluene (46 g., 0.5 mole), phosphorus trichloride (275 g., 2.0 moles) and aluminum chloride (67 g., 0.5 mole; the sublimed grade of aluminum chloride supplied by the Ohio-Apex Company was found to be most suitable for this reaction) were gently refluxed with stirring for four hours and the reaction mixture was converted to diethyl toluenephosphonates as outlined earlier.[2b] The product distilled through a 15-plate column was obtained as a colorless liquid which boiled at 103–104° at 0.4 mm. Samples taken at the beginning and at the end of the distillation had the same refractive index ($n^{15}\mathrm{D}$ 1.4988). The yield of the ester was 77 g. (67.5%). Allowing the hold-up in the still, the actual yield was estimated to be 73%.

The product was hydrolyzed by refluxing with a large excess of hydrochloric acid overnight. The resulting material was taken up in 850 ml. of hot water and concentrated until crystallization began. On cooling, the first crop of crude para isomer was separated and the mother liquor was concentrated until a second portion of product began to crystallize. This was separated and the mother liquor was concentrated to approximately 50 ml. and chilled. A third crop of crude para isomer was then taken. The crude para derivative from these operations was combined and crystallized three times from water, until a constant melting point of 194–195° was attained. In all, 31 g. of the para isomer was obtained. The residual mother liquors were evaporated to dryness and the residue was treated with 500 ml. of boiling benzene, leaving behind a small amount of crude para isomer, which was separated. Evaporation of the benzene solution yielded an amorphous gum which was subjected to systematic fractional crystallization. The product was dissolved in 300 ml. of hot chloroform and 5–10 ml. of ethanol. The solution was cooled to room temperature with stirring and the precipitated solid was filtered off. The mother liquor was mixed with an equal volume of dry toluene, followed by 20–25 ml. of dry benzene and the more volatile solvents were allowed to evaporate slowly at room temperature for 24–48 hours. The precipitated material was collected and subjected to the same procedure as outlined above. The less soluble fractions were combined in pairs for subsequent crystallization, as were the more soluble fractions. In all, twelve stages of fractional crystallization were necessary to secure an adequate separation of the isomers. The separated isomers were finally crystallized from chloroform–benzene mixture. There were obtained 13.5 g. of *m*-toluenephosphonic acid and 5.0 g. of *o*-toluenephosphonic acid. The reference conpounds, used for mixed melting point determinations, were prepared by the Grignard method of Burger and Dawson.[6]

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(1) A. Michaelis, *Ber.*, **12**, 1009 (1879); A. Michaelis and C. Panek, *Ber.*, **13**, 653 (1880); *Ann.*, **212**, 203 (1882); and subsequent papers.

(2) (a) W. T. Dye, THIS JOURNAL, **70**, 2595 (1948); (b) G. M. Kosolapoff and W. F. Huber, *ibid.*, **69**, 2020 (1947).

(3) G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 45–46; "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, pp. 300–301.

(4) B. Buchner and L. B. Lockhart, THIS JOURNAL, **73**, 755 (1951).

(5) R. H. Wiley and C. H. Jarboe, *ibid.*, **73**, 4996 (1951).

(6) A. Burger and N. D. Dawson, *J. Org. Chem.*, **16**, 1250 (1951).

The ortho isomer melted at 140–141°, the meta isomer at 121–122°. The latter was previously prepared by Michaelis; m.p. 116–117°.[7]

b.—The composition of the reaction mixture was the same as in (a), but the product was worked up by Dye's method.[2a] The aluminum chloride was precipitated with phosphorus oxychloride and the toluenedichlorophosphines were extracted with petroleum ether. Concentration of the solution gave the crude product in 74% yield. This was converted to the phosphonous acids by treatment with ethanol and water.[8]

The product was an uncrystallizing oil, thus immediately suggesting the presence of an isomeric mixture. The crude mixture was oxidized by heating for four hours with a large excess of mercuric chloride in two liters of water. The mixture was treated with hydrogen sulfide to remove the mercury ions and the filtrate was concentrated to approximately 500 ml. The hot solution was treated with excess lead oxide, stirred for two hours and filtered. The solid material, composed of unreacted lead oxide and lead salts of the toluenephosphonic acids, was suspended in two liters of water with stirring and the mixture was saturated with hydrogen sulfide. The filtrate was worked up as outlined under (a). There was obtained 28 g. of pure *p*-toluenephosphonic acid and 17 g. of the benzene-soluble mixture of the ortho and the meta isomers. A five-gram portion of this mixture, which melted at 100–123°, was subjected to fractional crystallization, as outlined under (a). In this way there was isolated 2 g. of the meta isomer and about 0.5 g. of the ortho isomer, thus confirming the findings under (a).

Ethylbenzene.—Only an exploratory trial of this compound was made. The hydrocarbon (0.5 mole) was treated as described under (a) above. There was isolated 52 g. of crude phosphonic acid. Crystallization of this from hot water yielded a total of 35 g. of the *p*-ethylbenzenephosphonic acid, which melted at 174.5–175.0°. Michaelis' reported a melting point of 164° for this substance. A similarly higher melting point of the *p*-toluene compound, in comparison with Michaelis' data, was recently reported by Doak and Freedman.[9] The residual material was soluble in benzene. It was repeatedly crystallized from the solvent mixture used in the separation of the toluene derivatives (see above). In this manner there was isolated some four grams of an ethylbenzenephosphonic acid which melted at 116–117°, presumably the more abundant *m*-isomer.

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(7) A. Michaelis, *Ann.*, **294**, 1 (1896).

(8) G. M. Kosolapoff and J. S. Powell, THIS JOURNAL, **72**, 4291 (1950).

(9) G. O. Doak and L. D. Freedman, THIS JOURNAL, **73**, 5658 (1951).

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[CONTRIBUTION FROM THE CANCER RESEARCH LABORATORY, UNIVERSITY OF FLORIDA]

Nitrogen Derivatives of Dibenzoselenophene[1]

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RECEIVED FEBRUARY 25, 1952

Dibenzoselenophene has been nitrated and the nitro derivatives reduced to the amino compound. The acetyl- and ethylurethan derivatives were then prepared. From a consideration of ultraviolet absorption spectra, it is concluded that nitration has occurred in the 2-position.

Derivatives of dibenzofuran and dibenzothiophene have been shown to be active carcinogens in the rat.[3] In work carried out in this Laboratory on these compounds and other derivatives of dibenzofuran and dibenzothiophene, it was necessary to investigate the chemistry of dibenzoselenophene.

From absorption spectra of dibenzothiophene and dibenzoselenophene, Fig. 1, one might predict that the chemical reactivities of the two molecules will be of the same order. In respect to nitration this was found to be true. Nitration of dibenzothiophene gave dibenzothiophene-5-oxide and 2-nitrodibenzothiophene.[4] The nitration of dibenzoselenophene gave a yellow crystalline nitrodibenzoselenophene. The structure of this compound is based on the spectral curves shown in this paper. Thus, the absorption spectra shown in Fig. 2 for 2-nitrodibenzothiophene and nitrodibenzoselenophene are almost identical. In Fig. 3 are shown the dissimilar curves of 2-carbethoxyaminodibenzothiophene and 3-carbethoxyaminodibenzothiophene.

Comparison of these curves with the absorption spectra of the carbethoxyamino derivative (Fig. 4) derived from nitrodibenzoselenophene points out the remarkable resemblance in the absorption spectra between 2-carbethoxyaminodibenzothiophene and the carbethoxyaminodibenzoselenophene. Substitution of a selenium atom for a sulfur atom in these compounds causes a hypochromic and a bathochromic shift for the large majority of wave length maxima.

On the basis of the evidence presented it is concluded that nitration of dibenzoselenophene gives 2-nitrodibenzoselenophene.

Experimental

Dibenzoselenophene.—Following the procedure of McCullough, *et al.*,[5] colorless crystals of this compound were obtained melting at 76–78° after vacuum distillation and recrystallization from hexane (reported[5] m.p. 73°).

2-Nitrodibenzoselenophene.—To a stirred solution of 3.4 g. of dibenzoselenophene in 20 ml. of acetic acid at approximately 65° was added slowly 1.5 ml. of fuming nitric acid (d. 1.5). After a few minutes standing, the clear dark yellow solution solidified to a yellow mush. After cooling, the mixture was filtered. Recrystallization from ethyl alcohol yielded 1.6 g. (40%) of lustrous yellow needles melting at 180°.

Anal. Calcd. for $C_{12}H_7NO_2Se$: C, 52.20; H, 2.54; N, 5.07. Found: C, 52.26; H, 2.54; N, 5.08.

2-Aminodibenzoselenophene.—To a hot solution of 3.6 g. of 2-nitrodibenzoselenophene in 90 ml. of acetic acid was added a solution of 16.5 g. of hydrated stannous chloride in 90 ml. of concentrated hydrochloric acid. The mixture was refluxed several hours. The clear colorless solution was cooled and then filtered. The crystals were suspended in

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(1) This investigation was supported by research grant C-1308 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(2) To be submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, University of Florida.

(3) E. C. Miller, J. A. Miller, R. B. Sandin and R. K. Brown, *Cancer Research*, **9**, 504 (1949).

(4) H. Gilman and J. F. Nobis, THIS JOURNAL, **71**, 274 (1949).

(5) J. D. McCullough, T. W. Campbell and E. S. Gould, *ibid.*, **72**, 5753 (1950).