[Contribution from the Chemical Laboratory of Iowa State College]

THE PRELIMINARY FORMATION OF ADDITION COMPOUNDS IN SUBSTITUTION REACTIONS OF AROMATIC TYPES. THE BROMINATION OF ETHYL 2-FURYLACRYLATE

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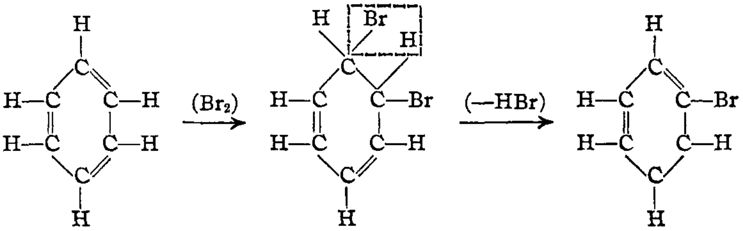
Introduction

Numerous explanations have been proposed to account for the mechanism of substitution reactions of aromatic compounds. Among these is that of Holleman,[1] postulating the formation of an intermediate addition compound which subsequently loses a hydrogen from the ring and a part of the addenda to give the ultimate substitution product. The following reaction may be taken by way of illustration of the bromination of benzene.



Two objections, in particular, have been raised against an interpretation of this kind. First, the preliminary addition compounds in such typical substitution reactions as halogenation, nitration, sulfonation, mercuration, arsonation, etc., have not been isolated. Second, if substitution did proceed via addition compounds, then such reactions should lead to the very ready formation of poly-substitution products, a conclusion which is not borne out by the readily controllable substitution reactions so characteristic of aromatic types. The expectancy of the facile formation of poly-substitution products appears reasonable to many in view of the fact that with the formation of the addition compound, the aromatic character is destroyed and the resulting dihydro-aromatic type should lend itself to the prompt formation of poly-addition compounds which in turn should yield poly-substitution products.

The first objection is not entirely valid. A part of it may be due to unfamiliarity with scattered references which may be proffered in support of preliminary addition. For example, the following observation[2] has

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[1] Holleman, "Die direkte Einführing von Substituenten in den Benzolkern," Leipzig, Veit and Co., 1910. In the illustration of the bromination of benzene, we might, of course, have 1,4-addition of bromine followed by 1,4-removal of hydrogen bromide.

[2] Muskat and Becker, This Journal, 52, 812 (1930). We must confess that we were unaware at first of all of the addition compounds referred to in our paper. It is certain that those which we have culled from a cursory examination of the literature are

just been made: "In studying the addition reactions of conjugated systems, we have a marked advantage over the study of similar reactions in the aromatic nucleus for it is possible to isolate the intermediate addition compound prior to its breakdown to the substitution derivative; in the reactions of aromatic compounds, only substitution products can as yet be isolated." The second objection has been tested recently by Van Alphen[3] and shown to lack validity, at least with Δ-2,6-dihydrophthalic acid.

The following references are pertinent to some of the illustration available in the literature which may be advanced in support of addition compounds being precursors of bromine substitution products: benzene,[4] naphthalene,[5] anthracene,[6] phenanthrene,[7] pyridine,[8] furan,[9] thiophene[10] and pyrrole.[11]

We are presenting at this time evidence for the preliminary addition of bromine to the furan nucleus incidental to the ultimate substitution of one of the nuclear hydrogens by bromine. It has long been known that some heterocyclic types like furan, thiophene and pyrrole have properties (physical, chemical and physiological[12]) which warrant their formal cor-

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far from being a complete list. A general account of addition preceding substitution may be found in Chapters IX and X of Johnson and Hahn's translation and enlargement of Henrich's "Theories of Organic Chemistry," Chapman and Hall, New York, **1922.**

[3] Van Alphen, *Rec. trav. chim.*, **47**, 169 (1928). This article contains references to related studies, and particularly to another type of addition (involving *one* and not two carbon atoms) proposed by Prins.

[4] Meunier, *Ann. chim. phys.*, [6] **10**, 223 (1887). Mitscherlich, *Poggendorff's Ann. Phys. Chem.*, **35**, 374 (1835).

[5] Laurent, *Ann. chim. phys.*, **59**, 196 (1835); **66**, 196 (1837); Orndorff and Moyer, *Am. Chem. J.*, **19**, 262 (1897).

[6] Laurent, *Ann.*, **34**, 295 (1840); Meyer and Jacobson, Vol. II, part 2, p. 516.

[7] Hayduck, *ibid.*, **167**, 177 (1873); Austin, *J. Chem. Soc.*, **93**, 1760 (1908); Henstock, *ibid.*, **119**, 55 (1921); **123**, 3097 (1923). The prior formation of phenanthrene dibromide has been confirmed frequently by Dr. Arthur J. Hill.

[8] Hofmann, *Ber.*, **12**, 988 (1879), and just recently Englert and McElvain, This Journal, **51**, 863 (1929). In these and related instances, it is definitely known that the bromine is initially attached to nitrogen. However, it is not definitely known whether the bromine subsequently adds to an ethylenic linkage.

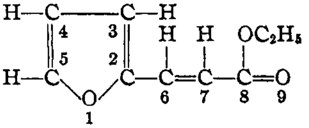
[9] Tönnies, *Ber.*, **11**, 1086 (1878); Schiff and Tassinari, *ibid.*, **11**, 842 (1878); Trefilev, *Ukrainskii Khem. Zhur.*, **1**, Sci. Pt., 121–296 (1925); [*C. A.*, **23**, 3926 (1929)].

[10] Whitmore, "Organic Compounds of Mercury," The Chemical Catalog Co., New York, **1921**, p. 36. This reference is to the general principle of preliminary addition. Very probably the initial step in bromination of sulfides at low temperatures is addition of the bromine molecule to sulfur. This is the case with diaryl sulfides [see Fries and Vogt, *Ann.*, **381**, 337 (1911)].

[11] The problem of preliminary addition to the nitrogen in pyridine probably applies to pyrrole. Too little, however, is known about these very unstable bromopyrroles. (See Hess and Wissing, *Ber.*, **48**, 1884 (1915).)

[12] Gilman and Pickens, This Journal, **47**, 245 (1925). Meyer and Jacobson, "Lehrbuch der Organischen Chemie," Vol. II, part 3, section I, pp. 12–17, contains a general critical account of the formulas of these compounds.

relation with benzene types. We have resolved a typical substitution reaction, the bromination of the furylacrylic nucleus, into two distinct steps: first, the addition of bromine to the ring, and then subsequent removal of hydrogen bromide. We previously demonstrated[13] that the substituted bromine occupies the 5-position.



This ethyl 5-bromofurylacrylate results definitely from a bromine addition compound, which subsequently loses hydrogen bromide. One atom of the bromine molecule[14] which added initially must have been attached to carbon 5. If addition occurred at one ethylenic linkage, then the other atom of bromine may have been on carbon 4, and this second atom of bromine subsequently combined with the hydrogen of carbon 5 to give hydrogen bromide and ethyl 5-bromofurylacrylate.

However, because of the multiple series of conjugated linkages in the ethyl furylacrylate, there are possibilities that the second bromine was attached (by 1,4-addition) to carbon 2 of the conjugated[15] system -(2,3,4,5); or (by 1,6-addition) to carbon 7 of the system -(7,6,2,3,4,5); or to oxygen 9 (by 1,8-addition) to the system -(9,8,7,6,2,3,4,5). This last we consider highly improbable.[16] A common interpretation would be addition to the 4,5-ethylenic linkage, although evidence with other reactions of the furan type under consideration makes it altogether likely that with some addenda we are dealing with 1,4- and with 1,6-additions. With 1,4-addition of bromine to the carbon atoms 2 and 5, it would only be necessary to have 1,4-removal of hydrogen bromide from carbon atoms 5 and 2. We are at present inclined to view the addition as 1,4-, partly because the second molecule of bromine apparently adds laterally to carbon atoms 6 and 7; because no ethyl 3- or 4-bromofurylacrylate has

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[13] Gilman and Wright, *Rec. trav. chim.*, **49**, 195 (1930).

[14] Possibly both bromine atoms may have been attached initially to carbon 5; see Ref. 3 of this paper.

[15] There are other theoretically possible conjugated systems, namely, those involving oxygen 1. If we assume that the oxygen is capable of functioning, latently or otherwise, in an oxonium form, then we have a hypothetical double bond emerging from this oxygen, and by virtue of such a condition, the conjugated systems -(1,5,4) and -(1,2,3) might be considered. However, neither of these would account (rearrangements excluded) for the attachment of bromine to carbon 5. In this connection, it is interesting to note that Moureu, Dufraisse and Johnson, *Ann. chim.*, **7**, 8 (1927) have postulated prior addition of bromine to the oxygen in a study of furylacrylic *acid*. This will be considered in a later report on the more extensive bromination of furylacrylic acid and its ethyl ester.

[16] Kohler and Butler, THIS JOURNAL, **48**, 1036 (1926); Lutz, *ibid.*, **51**, 3008 (1929).

been isolated; and, finally, because polynuclear substitution takes place with great difficulty when the hydrogens attached to carbon atoms 2 and 5 have been replaced.

Experimental Part

The ethyl furylacrylate was prepared in accordance with the improved directions of Gilman, Brown and Jones.[17]

To 83 g. (0.5 mole) of ethyl furylacrylate in 200 cc. of dry carbon disulfide there was added dropwise and with constant stirring 80 g. (0.5 mole) of bromine in 50 cc. of carbon disulfide. One experiment was carried out at room temperature and another at $-15°$. The crystals which separated on chilling this solution to about $-10°$ weighed 51 g., or 31% of the theoretical amount for the dibromide, and melted at 60°. When crystallized at a low temperature (-80 to 20°) from petroleum ether (b. p. 40–80°), the compound melted at 70°. Because of the high instability of the dibromide, it was analyzed immediately.

Anal. Calcd. for $C_9H\,O_3Br_2$: Br, 49.08. Found: Br, 49.15.

The same compound was also prepared after the technique employed by Moureu, Dufraisse and Johnson[18] for the bromination of furylacrylic acid. To 41.5 g. (0.25 mole) of the ester in 100 cc. of chloroform was added slowly 40 g. (0.25 mole) of bromine. This reaction was carried out at $-15°$ in an atmosphere of carbon dioxide which was circulated through a 500-cc. three-necked flask provided with a stirrer, dropping funnel and thermometer. When addition was completed, most of the solvent was removed at room temperature and under reduced pressure. The crystals which formed were separated by filtration and washed with a small quantity of petroleum ether. The yield of compound melting at 60° was 30 g. The compound was recrystallized from petroleum ether by dissolving it at room temperature and cooling to $-80°$. The compound so obtained showed no depression in a mixed melting point determination with the dibromide prepared in carbon disulfide. During the crystallization about one-half of the original product did not dissolve in petroleum ether and this compound was identified as ethyl 5-bromo-2-furyl dibromopropionate, the acid of which was described previously by Gibson and Kahnweiler.[19] There appears to be less decomposition in the addition of bromine in a carbon disulfide solution.

When the dibromo addition compound was dissolved in alcohol and treated with zinc dust, the bromine atoms were removed and ethyl furylacrylate was obtained. The dibromo ester, dissolved in either chloroform or alcohol, appears to be unaffected by mercury.

A solution containing 6.5 g. (0.02 mole) of the dibromo ester in alcohol was treated with alcoholic potassium hydroxide until the mixture was alkaline. The potassium bromide (determined by silver bromide) obtained by filtration was 97.5% of the theoretical quantity. The filtrate was heated with dilute sodium hydroxide in order to hydrolyze the ester to the more readily workable acid. Acidification of this hydrolysate, subsequent to decolorization by Norite, yielded 5-bromofurylacrylic acid, which was identified by a mixed melting point determination with an authentic specimen.[18]

When the dry dibromo compound is permitted to decompose spontaneously (accompanied by the evolution of hydrogen bromide), very small quantities of 5-bromofurylacrylic acid can be isolated by the subsequent hydrolysis of the oil.

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[17] Gilman, Brown and Jones, *Iowa State Coll. J. of Science*, **2**, 317 (1928).

[18] Moureu, Dufraisse and Johnson, *Ann. chim.*, **7**, 8 (1927).

[19] Gibson and Kahnweiler, *Am. Chem. J.*, **12**, 314 (1890).

Summary

When ethyl furylacrylate is treated with bromine, an unstable dibromo addition compound is formed which readily loses hydrogen bromide to give ethyl 5-bromofurylacrylate. The isolation and analysis of this intermediate dibromo compound is advanced as supplementary evidence for the prior formation of addition compounds in substitution reactions of aromatic types.

AMES, IOWA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ALBERTA]

SOME DERIVATIVES OF DIPHENYL SULFIDE AND DIPHENYL ETHER

BY REUBEN B. SANDIN AND WRAY V. DRAKE

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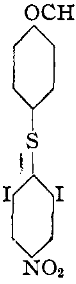
The importance of the diaryl sulfide and diaryl oxide groupings in compounds which have therapeutic value has been demonstrated in the important work of T. B. Johnson[1] and C. R. Harington,[2] respectively. For this reason it was considered of interest to synthesize some sulfur ether analogs (Formula I) of 2,6-di-iodo-4-nitro-4′-methoxydiphenyl ether and its reduction compound 2,6-di-iodo-4-amino-4′-methoxydiphenyl ether. The latter compounds are intermediates in Harington and Barger's synthesis of thyroxine.[2] It was also considered of importance to prepare some oxygen ether isomers (Formulas II and III) of the above-mentioned compounds, *viz.*, 2,6-di-iodo-4-nitro-3′-methoxydiphenyl ether, 2,6-di-iodo-4-nitro-2′-methoxydiphenyl ether and the corresponding amino compounds.

The ultimate aim in view was to synthesize a sulfur ether analog of thyroxine[3] and also two oxygen ether isomers of thyroxine. Because this



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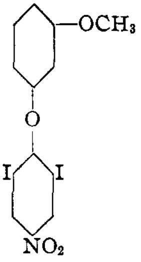

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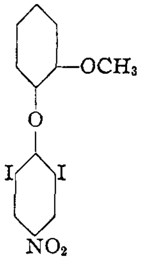

III

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[1] Hilbert and Johnson, THIS JOURNAL, **51**, 1526 (1929); Bass and Johnson, *ibid.*, **52**, 1146 (1930).

[2] Harington, *Biochem. J.*, **20**, 293, 300 (1926); Harington and Barger, *ibid.*, **21**, 169 (1927).

[3] This work is now in progress.