In a second experiment, carbonation at the end of fifteen minutes gave a 50% yield of crude *p*-methoxybenzoic acid, melting at 170–174°. From a third experiment in which the reaction mixture was heated at 50° in a 1:1 ether–benzene solvent for five hours, the yield of pure 5-iodo-2-methoxybenzoic acid was 24%.

Orienting experiments have shown that it is possible to metalate alcohols (like benzyl alcohol), phenols, and primary and secondary amines. Also, halogen–metal interconversions take place with a variety of bromo and iodo compounds containing, in addition, other functional groups like amino, hydroxy, and acids and their derivatives. For example, *o*-bromophenol and *n*-butyllithium give, subsequent to carbonation and hydrolysis, a 60% yield of salicylic acid; and under corresponding conditions *o*-bromoaniline gives a 36% yield of anthranilic acid.

Summary

It has been shown that the metalations reported previously of some halogenated ethers involve a two-stage procedure. First, there is a halogen–metal interconversion, and, second, the organometallic compound formed in this manner then metalates the original halogenated ether. The interconversion reaction is more rapid. For example, in fifteen minutes, 2-bromodibenzofuran reacts with *n*-butyllithium to give excellent yields of 2-dibenzofuryllithium. Upon protracted refluxing, this RLi compound then metalates 2-bromodibenzofuran to give 2-bromo-4-dibenzofuryllithium.

Related observations are reported with *p*-bromoanisole and *p*-iodoanisole.

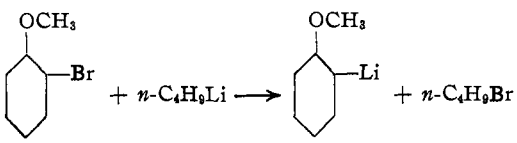
AMES, IOWA
GOODWELL, OKLAHOMA RECEIVED DECEMBER 7, 1939

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

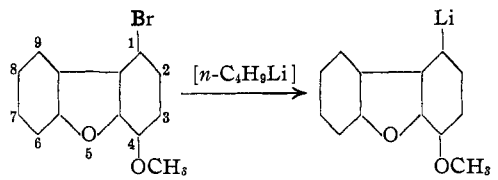
Dibenzofuran. XVII. The Reaction of Bromo-Ethers with *n*-Butyllithium[1]

BY HENRY GILMAN, JACK SWISLOWSKY AND GEORGE E. BROWN

The recent availability of a series of bromomethoxy derivatives of dibenzofuran has provided essential material for an examination of the scope of halogen–metal interconversion reactions. In the first published illustrations of this reaction with bromo-ethers,[2] the bromine replaced by lithium was always *ortho* to an ether linkage. A typical simple illustration is



We are now reporting reactions of *n*-butyllithium with a series of bromomethoxydibenzofurans in which the bromine atoms are disposed in most of the important positions with respect to the ether linkages. In these eight compounds, a bromine atom is not only *ortho*, *meta* and *para* to a methoxy group, but also *ortho* and *meta* to the oxygen bridge in dibenzofuran. We have found that in every case the predominant reaction is a halogen–metal interconversion.



Some of the reactions reported are synthetically valuable. For example, 1-bromo-3,4-dimethoxydibenzofuran has not as yet yielded either an organomagnesium[3] or an organolithium[4] compound when treated with the respective metals under general conditions for the formation of these organometallic compounds. However, *n*-butyllithium reacts promptly with 1-bromo-3,4-dimethoxydibenzofuran to give a satisfactory yield of 3,4-dimethoxy-1-dibenzofuryllithium.

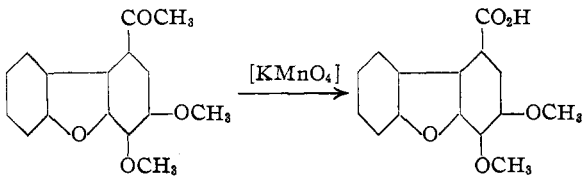
The structures of the several reaction products were established by conventional procedures involving carbonation to the corresponding acids which were in turn compared with authentic specimens. The acid resulting from 1-bromo-3,4-dimethoxydibenzofuran was shown to be identical with 3,4-dimethoxy-1-dibenzofurancarboxylic acid prepared as follows

(1) Paper XVI, THIS JOURNAL, **62**, 346 (1940).

(2) General references on this reaction are contained in the accompanying papers: (a) Gilman and Banner, *ibid.*, **62** 344 (1940), and (b) Gilman, Langham and Willis, *ibid.*, **62**, 346 (1940).

(3) The activated magnesium–copper alloy was not used.

(4) Gilman, Zoellner and Selby, THIS JOURNAL, **55**, 1252 (1933).



Experimental Part

1-Bromo-2-methoxydibenzofuran.—A solution of *n*-butyllithium, prepared from 4.15 g. (0.03 mole) of *n*-butyl bromide and 0.5 g. (0.07 g. atom) of lithium in 20 cc. of ether, was added at once to 2.77 g. (0.01 mole) of 1-bromo-2-methoxydibenzofuran[5] in 40 cc. of warm benzene. A white precipitate formed immediately and the solvent began to reflux gently. Heat was applied, and after ten minutes of refluxing with stirring the mixture was carbonated by addition to solid carbon dioxide. After removal of the solvent by distillation the residue was extracted with hot potassium hydroxide solution, from which was obtained 1.8 g. (73.5%) of acid melting at 135–140°. Two recrystallizations from dilute ethanol gave 1.15 g. (47%) of acid melting at 155–157°. A mixed melting point with an authentic sample of 2-methoxy-1-dibenzofurancarboxylic acid (m. p., 156–157°)[6] showed no depression. The methyl ester, prepared from the acid and diazomethane in ether, melted at 100° and did not depress the melting point of an authentic sample of methyl 2-methoxy-1-dibenzofurancarboxylate (m. p. 99.5–100°).[6]

1-Bromo-4-methoxydibenzofuran.—A solution of *n*-butyllithium prepared from 0.11 g. (0.16 g. atom) of lithium and 10 g. (0.073 mole) of *n*-butyl bromide in 50 cc. of dry ether was filtered rapidly into a solution of 13.85 g. (0.05 mole) of 1-bromo-4-methoxydibenzofuran in 100 cc. of dry benzene. A gray precipitate formed immediately. The suspension was refluxed with stirring for one-half hour, and then carbonated by pouring upon crushed solid carbon dioxide. On working up the mixture in a customary manner there was obtained 8.3 g. (68.5%) of 4-methoxy-1-dibenzofurancarboxylic acid (m. p. 278°). Identification was completed in two ways: first, by a mixed melting point determination with an authentic specimen of the acid; and, second, by conversion to methyl 4-methoxy-1-dibenzofurancarboxylate and comparison of this ester with one prepared from an authentic specimen of the corresponding acid.[7]

Methyl 4-Methoxy-1-dibenzofurancarboxylate.—Addition of an excess of diazomethane solution to a suspension of 0.1 g. of 4-bromo-1-dibenzofurancarboxylic acid in ether gave a quantitative yield of methyl 4-methoxy-1-dibenzofurancarboxylate. This ester melted at 125° after crystallization from methanol.

Anal. Calcd. for $C_{15}H_{12}O_4$: methoxyl, 24.22. Found: methoxyl. 24.18.

3-Bromo-2-methoxydibenzofuran.—An ether solution of *n*-butyllithium (0.015 mole) was added in one portion to 1.39 g. (0.005 mole) of 3-bromo-2-methoxydibenzofuran[5] in 60 cc. of warm benzene. The mixture was stirred and refluxed for fifteen minutes and then carbonated. The 2-methoxy-3-dibenzofurancarboxylic acid isolated melted at 197–199° and weighed 0.710 g. (58.6%). Recrystallization from glacial acetic acid yielded 0.490 g. (40.5%) of acid melting at 206–207°. A mixed melting point with an authentic specimen of the acid (m. p. 206–207°)[5] showed no depression. The methyl 2-methoxy-3-dibenzofurancarboxylate obtained from the acid resulting from the interconversion reaction was shown to be identical with an authentic specimen.[8]

In another experiment in which only one-half the amount of *n*-butyllithium was used and where the time of refluxing was ten minutes, the yield of crude acid was 24.5%.

6-Bromo-4-methoxydibenzofuran.—To 60 mg. (0.000216 mole) of 6-bromo-4-methoxydibenzofuran[8] dissolved in 2.4 cc. of warm benzene was added 1.2 cc. of an ether solution of *n*-butyllithium (0.0005 mole), and the solution was stirred and heated. Just before the boiling point was reached, a white precipitate appeared which gradually became heavier. Carbonation was carried out at the end of fifteen minutes. There was obtained 30 mg. (57.4%) of crude acid which sintered at 210° and melted at 223–225° with decomposition. The pure 4-methoxy-6-dibenzofurancarboxylic acid melts at 243–245°.[9]

The methyl ester prepared from the acid and diazomethane did not depress the melting point of authentic methyl 4-methoxy-6-dibenzofurancarboxylate (m. p. 123–124°).

1-Bromo-3,4-dimethoxydibenzofuran.—A mixture prepared from *n*-butyllithium (0.03 mole) in ether and 4.6 g. (0.015 mole) of 1-bromo-3,4-dimethoxydibenzofuran[8] in 100 cc. of benzene was refluxed with stirring for one-half hour. Carbonation gave 2.22 g. (54%) of acid melting at 234–235°. Crystallization from ethanol yielded needles melting at 236°. The acid was shown to be 3,4-dimethoxy-1-dibenzofurancarboxylic acid by the method of mixed melting points. In addition, the methyl ester was shown by the same process to be identical with an authentic specimen prepared by the oxidation of 1-acetyl-3,4-dimethoxydibenzofuran followed by methylation.[8,10]

3,4-Dimethoxy-1-dibenzofurancarboxylic Acid.—A suspension of 0.27 g. (0.001 mole) of 1-acetyl-3,4-dimethoxydibenzofuran in 75 cc. of water was oxidized by alkaline permanganate to give a 50% yield of 3,4-dimethoxy-1-dibenzofurancarboxylic acid. The acid melted at 236° after crystallization from ethanol.

Anal. Calcd. for $C_{15}H_{12}O_5$: methoxyl, 22.79. Found: methoxyl, 22.40.

Methyl 3,4-Dimethoxy-1-dibenzofurancarboxylate.—This ester was prepared in a quantitative yield from the corresponding acid and diazomethane. On crystallization from dilute ethanol the ester melted at 78°.

Anal. Calcd. for $C_{16}H_{14}O_5$: methoxyl, 32.55. Found: methoxyl, 32.40.

1-Bromo-4,6-dimethoxydibenzofuran.—An ether solution of 0.008 mole of *n*-butyllithium was added to a solution of 2.15 g. (0.007 mole) of 1-bromo-4,6-dimethoxydibenzofuran[11] in 60 cc. of benzene. After refluxing and

(5) Kindly provided by P. R. Van Ess.
(6) Kindly provided by R. L. Bebb.
(7) Gilman, Parker, Bailie and Brown, THIS JOURNAL, **61**, 2838 (1939).
(8) Kindly provided by L. C. Cheney.
(9) Unpublished studies by T. H. Cook.
(10) Gilman and Cheney, THIS JOURNAL, **61**, 3149 (1939).
(11) Kindly provided by T. H. Cook.

stirring for one-half hour, the mixture was carbonated to give a 60% yield of acid melting at 296°. The identity of the acid as 4,6-dimethoxy-1-dibenzofurancarboxylic acid was established by converting it to the methyl ester and comparing this ester with an authentic specimen.[10]

1,9 - Dibromo - 2,8 - dimethoxydibenzofuran.—This dibromo compound was prepared by bromination of 2,8-dihydroxydibenzofuran and subsequent methylation.[12] The 1,9-positions of the bromine atoms are assigned provisionally on the basis of the behavior of the related 2-hydroxydibenzofuran upon bromination.[13]

To 1.5 g. (0.00389 mole) of the dibromo compound dissolved in 120 cc. of benzene was added an ether solution of *n*-butyllithium (0.035 mole). The mixture was refluxed and stirred for two hours and then carbonated to yield 820 mg. (66.6%) of acid melting at 210–220°. Two recrystallizations from glacial acetic acid raised the melting point to 270–271°, and a mixed melting point with the acid obtained from direct dimetalation of 2,8-dimethoxydibenzofuran[12] followed by carbonation was not depressed. The methyl ester, prepared from the acid, methanol and dry hydrogen chloride melted at 128–129° after crystallization from methanol.

This dimethyl 2,8-dimethoxy-1,9-dibenzofurandicarboxylate did not depress the melting point of the dimethyl ester[12] obtained from the 2,8-dimethoxydibenzofurandicarboxylic acid resulting from direct dimetalation of 2,8-dimethoxydibenzofuran.

3,7-Dibromo-2,8-dimethoxydibenzofuran.—To 0.7 g. (0.00183 mole) of the dibromo-2,8-dimethoxydibenzofuran melting at 260–261° and tentatively designated as the 3,7-isomer,[12] dissolved in 60 cc. of benzene was added an ether solution of 0.018 mole of *n*-butyllithium. After stirring and refluxing for seven hours, the mixture was carbonated. The resulting acidic material weighed 650 mg. and from this was isolated by sublimation several tenths of a gram of benzoic acid.[14] The residual acid, 2,8-dimethoxy-3,7-dibenzofurandicarboxylic acid, was recrystallized three times from glacial acetic acid to yield 0.1 g. (17.5%) of needles which melted at 290° with decomposition.

Anal. Calcd. for $C_{16}H_{12}O_7$: methoxyl, 19.62. Found: methoxyl, 19.62.

Thirty milligrams of the dimethoxy-dibasic acid was esterified by methanol and dry hydrogen chloride to yield 18 mg. (50%) of dimethyl 2,8-dimethoxy-3,7-dibenzofurandicarboxylate. This ester crystallized from methanol as needles melting at 183–184°.

Anal. Calcd. for $C_{18}H_{16}O_7$: methoxyl, 36.05. Found: methoxyl, 36.50.

(12) Unpublished studies.

(13) Gilman and Van Ess, THIS JOURNAL, **61**, 1365 (1939).

(14) It is known that benzene and *n*-butyllithium give on protracted refluxing small quantities of phenyllithium, the carbonation of which yields benzoic acid.

AMES, IOWA RECEIVED DECEMBER 7, 1939

Summary

The halogen–metal interconversion reaction has been shown to be the predominant reaction with a series of bromo-ethers of dibenzofuran in which a bromine is not only *ortho*, *meta* and *para* to a methoxy group, but also *ortho* and *meta* to the oxygen bridge.

Although no organomagnesium or organolithium compound can be prepared from 1-bromo-3,4-dimethoxydibenzofuran with magnesium or lithium, respectively, under ordinary conditions, a reaction takes place readily and satisfactorily with *n*-butyllithium to give 3,4-dimethoxy-1-dibenzofuryllithium.

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, NO. 754]

The Synthesis of 3,5-Difluoro- and 3-Fluoro-5-iodo-*dl*-tyrosine

BY JAMES ENGLISH, JR., JAMES F. MEAD AND CARL NIEMANN

Tyrosine and thyronine are different from all other amino acids in that they alone are found in nature as nuclear substituted halogen derivatives and in all cases it has been observed that the halogen atoms are contiguous to either a phenolic or aryloxy group.[1] Until recently the only halogenated amino acid of unambiguous physiological importance was the hormone thyroxine. However, the synthesis of 3-fluorotyrosine by Schiemann and Winkelmuller[2] and the subsequent pharmacological investigations of G. Litzka, K. Kraft, and W. May[3] have shown that other halogenated amino acids must be added to this category. As part of a study on the halogenated tyrosines and thyronines this communication describes the synthesis of 3,5-difluoro- and 3-fluoro-5-iodo-*dl*-tyrosine.[4]

(1) (a) C. R. Harington, *Fortschritte Chem. organ. Naturstoffe*, **2**, 103 (1939); (b) C. L. A. Schmidt, "The Chemistry of the Amino Acids and Proteins," C. Thomas, Springfield, Ill., 1938.

(2) G. Schiemann and W. Winkelmuller, *J. prakt. Chem.*, **135**, 101 (1932).

(3) (a) G. Litzka, *Arch. exptl. Path. Pharmakol.*, **183**, 427, 436 (1936); (b) *Klin. Wochschr.*, **15**, 1568 (1936); (c) *Z. ges. exptl. Med.*, **99**, 518 (1936); (d) *Deut. med. Wochschr.*, **63**, 1037 (1937); (e) H. May and G. Litzka, *Z. Krebsforsch.*, **48**, 376 (1939); (f) K. Kraft, *Z. physiol. Chem.*, **245**, 58 (1936); (g) K. Kraft and R. May, *ibid.*, **246**, 233 (1937); (h) W. May, *Klin. Wochschr.*, **14**, 790 (1935); **16**, 562 (1937).

(4) This research is being conducted as a coöperative project with Professor Paul Phillips of the University of Wisconsin.