[Contribution from the Chemical Laboratory of Iowa State College]

CARBAZOLE. I. SELECTIVE METALATION

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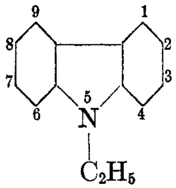
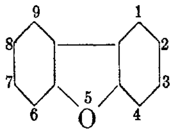
INTRODUCTION

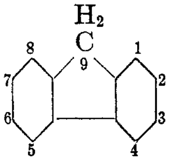
The hydrogen of an aromatic nucleus (in a parent or unsubstituted aromatic cycle) which is replaceable by metal appears to be independent of the metal and of the metalating agent. For example, metalation of dibenzofuran (II) gives a 4-metallo derivative



I



II



III

when the metal is lithium, sodium, potassium, calcium or mercury, or when the metalating agent is an organometallic compound, an inorganic salt like mercuric acetate, or a metal.[1] However, we have found that in the metalation of 5-ethylcarbazole (I) the hydrogen replaced depends on the metal which is introduced. Metalation by means of organoälkali compounds introduces the alkali metal in the 4-position; but metalation by mercuric acetate introduces the mercuri group in the 2-position. With the somewhat related cycle, fluorene (III), mercuration in acetic acid takes place in the 4-position and mercuration with no solvent involves both the 3- and the 4-positions.[2]

The structures of 5-ethylcarbazole-4-carboxylic acid and carbazole-4-carboxylic acid obtained by carbonation of the alkali-metalated 5-ethyl-

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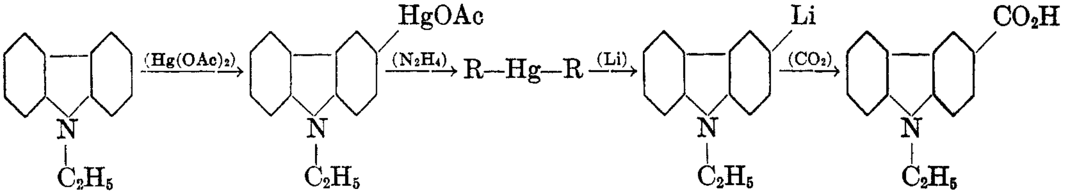
[1] Gilman and Young, *J. Am. Chem. Soc.*, **56**, 1415 (1934) and *ibid.*, **57**, 1121 (1935). See Gilman and co-workers, *Rec. trav. chim.*, **55**, 79 (1936) for metalation by means of phenylcalcium iodide.

[2] Miller and Bachman, *J. Am. Chem. Soc.*, **57**, 2447 (1935).

carbazole and carbazole, respectively, were established by comparison with authentic specimens of the acids. Carbazole-4-carboxylic acid was prepared by the procedure of Ciamician and Silber[3] from carbazole, potassium hydroxide and carbon dioxide. This acid was 5-ethylated[4] to give an acid identical with that obtained by alkali-metalation of 5-ethylcarbazole.

5-Ethylcarbazole was mercurated by mercuric acetate in ethanol and by fusion with mercuric acetate. In each case a mixture of mono- and dimercurials was obtained. The constitution of the monomercurial was established by replacing the mercuri group by iodine to give the known 5-ethyl-2-iodocarbazole.[4,5] The apparently anomalous site of mercuration suggested the desirability of ruling out the possibility that replacement of the mercuri group by iodine may have involved two separate and, in a sense, conflicting reactions: (1) replacement of the mercuri group by hydrogen; and (2) iodination of the resulting non-mercurated carbazole. It is known that direct iodination of 5-ethylcarbazole gives 5-ethyl-2-iodocarbazole;[5] accordingly, if reaction (1) occurred, the position of iodine would have no necessary bearing on the position of the initial mercuri group. With this difficulty in view, the mercurial was converted smoothly and in excellent yield by the hydrazine hydrate method[6] to the bis-mercurial, which with lithium gave the corresponding organolithium compound; and this organometallic compound when carbonated yielded 5-ethylcarbazole-2-carboxylic acid:



The constitution of the 2-carboxylic acid was established by three methods. (1) 5-Ethyl-2-iodocarbazole[5] was converted to the corresponding Grignard reagent which was carbonated; (2) the organolithium compound from

[3] Ciamician and Silber, *Gazz. chim. ital.*, **12**, 272 (1882). The structure of this acid was established subsequently by Briscoe and Plant, *J. Chem. Soc.*, **1928**, 1990, by sulfur-dehydrogenation of 1,2,3,4-tetrahydrocarbazole-6-carboxylic acid, which was obtained by ring closure.

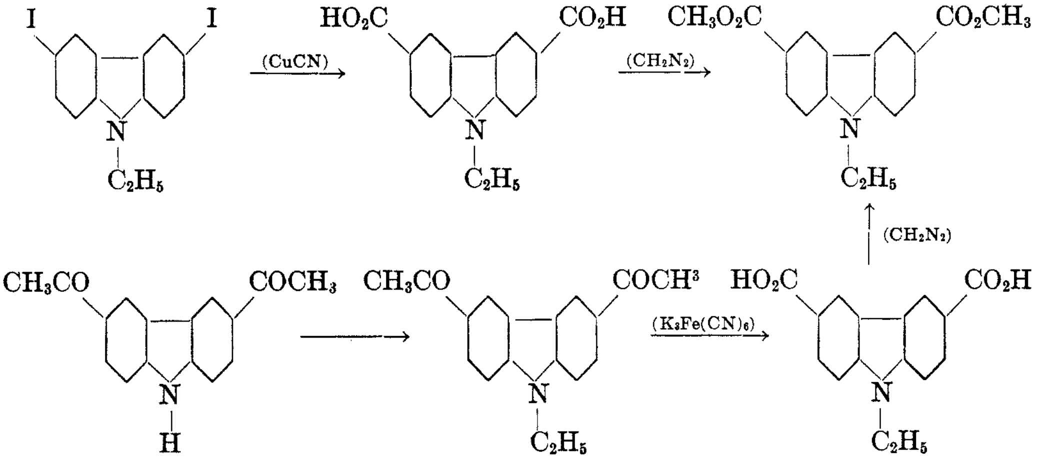
[4] In accordance with the procedure of Stevens and Tucker, *J. Chem. Soc.*, **123**, 2140 (1923).

[5] Tucker, *ibid.*, **1926**, 546.

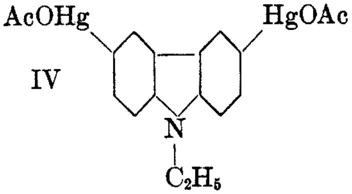
[6] Gilman and Barnett, *Rec. trav. chim.*, **55**, (July, 1936).

5-ethyl-2-bromocarbazole* was carbonated; and (3) carbazole-2-carboxylic acid[7] was ethylated to 5-ethylcarbazole-2-carboxylic acid.

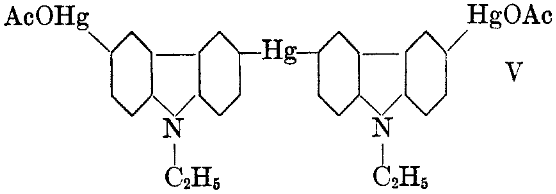
The dimercurial was shown to have mercuri groups in the 2- and 8-positions, for on replacement of the mercuri groups by iodine there resulted 5-ethyl-2,8-diïodocarbazole. This diïodo compound was prepared earlier by Tucker[5] who correctly assumed the positions of the iodines. The constitution of the diïodo compound was established by the following sequence of reactions, the structure of the 5-ethyl-2,8-diacetylcarbazole having been proved recently by Plant and co-workers[8] by means of ring closure.



Because of difficulties in the purification of the dimercurial it is not known whether the diïodo compound was obtained from either or both of the following possible compounds:



IV



V

Cechetti and Sarti[9] were the first to mercurate carbazole, and although

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* 5-Ethyl-2-bromocarbazole was prepared by the bromination of 5-ethyl-carbazole. The structure of 2-bromocarbazole was established by TUCKER, *J. Chem. Soc.*, **125**, 1144 (1924), and although this compound was known to give 5-ethyl-2-bromocarbazole, it had not been established hitherto that bromination of 5-ethylcarbazole gave 5-ethyl-2-bromocarbazole.

[7] Prepared in accordance with the directions of PLANT AND WILLIAMS, *J. Chem. Soc.*, **1934**, 1142, by oxidation of 2-acetylcarbazole.

[8] PLANT, ROGERS AND WILLIAMS, *J. Chem. Soc.*, **1935**, 741.

[9] CECHETTI AND SARTI, *Gazz. chim. ital.*, **60**, 189 (1930); [*C. A.*, **24**, 3787 (1930)].

they did not establish the structures of their compounds they indicate that the dimercurated compound may have a bis-mercurial constitution.

DISCUSSION OF RESULTS

If we confine consideration to metalation of one aromatic cycle of a polynuclear type it is clear that metalation can be selective in some cases and that the same hydrogen is not always replaced by any metal or its equivalent. Accordingly, there is no justification for using metalation as a criterion of the so-called acidity of aromatic hydrogens. It may be that some specific metalating agents can be used for this purpose. There are now available three chief classes of metalating agents: (1) organometallic compounds; (2) inorganic compounds like mercuric acetate; and (3) metals.

The rate of metalation depends, among other factors, on the carbon-hydrogen linkage and on the metalating agent. First, if we omit non-aromatic hydrogens like those attached to oxygen, nitrogen, sulfur, and true acetylenes, and activated hydrogens like those in the 9-position of fluorene (all of which react moderately rapidly to violently) we observe that the decreasing order of metalation is: dibenzofuran, 5-ethylcarbazole, 5-lithiumcarbazole. Second, the rate of metalation by means of organometallic compounds depends on both the R group and the metal, and appears to follow the general order of relative reactivity of organometallic compounds: the probable order of decreasing activity being RK, RNa, RLi, RCaI, RMgX.[10] Third, the rates of metalation of a series of aromatic compounds by inorganic salts do not follow the rates of metalation of the same series by organometallic compounds: for example, 5-ethylcarbazole is mercurated more readily than dibenzofuran. Also, the rates of metalation by metals appear to parallel the rates of metalation by organometallic compounds, but there is not now available sufficient evidence to warrant any definite conclusion. Fourth, not only do supposedly related polynuclear types metalate in different positions, but a selected polynuclear type may metalate in different positions depending upon nuclear substituents. For example, all types of metalating agents react in the 4-position of dibenzofuran; however, metalation of 2-methoxydibenzofuran, by means of RLi compounds, involves the 1- and the 3-positions.[11]

EXPERIMENTAL

Metalation of carbazole.—A clear, yellow solution containing 3.9 g. (0.02 mole) of carbazole in ether and 0.055 mole of *n*-butyllithium was refluxed for 20 hours and

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[10] Gilman and Nelson, *Rec. trav. chim.*, **55**, 518 (1936).

[11] Studies by R. L. Bebb.

then carbonated with solid carbon dioxide. There was isolated 0.05 g. of carbazole-4-carboxylic acid. The recovery of 2 g. of carbazole and the pronounced odor of *n*-valeric acid indicated a highly restricted reaction. Actually, the 4-acid may have come in part, at least, from a rearrangement reaction of the 5-lithium compound during carbonation.

Metalation of 5-ethylcarbazole.—To a clear ether solution (125 cc.) containing 0.06 mole of *n*-butyllithium (prepared from *n*-butyl chloride) was added 9.75 g. (0.05 mole) of 5-ethylcarbazole. After refluxing for 18 hours, the mixture was carbonated by solid carbon dioxide to give 2.2 g., or 23%, of acid, which is soluble in benzene, ethanol and carbon tetrachloride. The product was purified by crystallization from carbon tetrachloride-petroleum ether mixtures and finally from carbon tetrachloride alone, and melted at 165°.

Neutralization equivalent: Calc'd, 239; Found, 241.

Anal. Calc'd for $C_{15}H_{13}NO_2$: C, 75.3; H, 5.44; N, 5.86.
Found: C, 75.1; H, 5.50; N, 6.03.

When the above experiment was repeated with the use of a larger excess of *n*-butyllithium (0.085 mole, and 0.03 mole of 5-ethylcarbazole), the yield of 5-ethylcarbazole-4-carboxylic acid was 22%, and no dicarboxylic acid was isolated.

No acid was isolated in an experiment involving 0.095 mole of ethylmagnesium bromide and 0.02 mole of 5-ethylcarbazole. Prior to carbonation the ether-toluene solution was heated at 85° for 20 hours. Ninety per cent. of the 5-ethylcarbazole was recovered.

Although no metalation occurred under the stated conditions with ethylmagnesium bromide, it does appear that the more reactive phenylcalcium iodide is somewhat effective. The acidic fraction (other than the benzoic acid from excess phenylcalcium iodide) has not yet been resolved. The 85% recovery of 5-ethylcarbazole is remindful of the definitely established but highly restricted metalation of dibenzofuran by phenylcalcium iodide.[1]

The acidic fractions obtained by metalating 5-ethylcarbazole by means of the ethyl- and *n*-butylsodium and -potassium compounds have not been identified as yet. In some of these cases there is evidence of dimetalation. The organolithium compounds are superior to the organosodium and -potassium compounds for monometalation of both 5-ethylcarbazole and dibenzofuran.

It is interesting to note in connection with relative acidities that after refluxing a suspension of 0.05 mole of 4-dibenzofurylpotassium with 0.05 mole of 5-ethylcarbazole for 24 hours, and then cooling to −5° and carbonating with carbon dioxide gas, there was isolated dibenzofuran-4-carboxylic acid free of carbazole acid. The experiment just described is perhaps as one might have predicted; however, the following experiment which indicates that benzene has a more acidic hydrogen than 5-ethylcarbazole is not as one might have predicted. To a solution of 0.03 mole of di-*n*-butylmercury in 100 cc. of benzene was added 2.1 g. (0.09 g. atom) of sodium, and the mixture was stirred at room temperature for 16 hours. 5-Ethylcarbazole (0.05 mole) was added to the resulting suspension, and the mixture was stirred for 8 hours, after which it was carbonated at 0°. There was isolated a 77% yield of benzoic acid, but no carbazole acid; and there must have been some unused *n*-butylsodium, as evidenced by the odor of valeric acid. It is quite possible in this latter experiment that the *n*-butylsodium had metalated the benzene prior to addition of the 5-ethylcarbazole; if this be the case, one might still have expected the phenylsodium to have metalated the 5-ethylcarbazole.

Constitution of 5-ethylcarbazole-4-carboxylic acid.—Two-tenths g. (0.001 mole) of carbazole-4-carboxylic acid was ethylated in acetone by means of diethyl sulfate and potassium hydroxide[4] (followed by hydrolysis) to give an 84% yield of crude 5-ethylcarbazole-4-carboxylic acid melting at 156–158°. Crystallization from carbon tetrachloride raised the melting point to 165°, and there was no depression in the melting point of a mixture of this product with the acid obtained from 5-ethylcarbazole and *n*-butyllithium.

Inasmuch as acids other than carbazole-4-carboxylic acid have been obtained from the carbonation of 5-potassiumcarbazole, the carbazole-4-carboxylic acid used in the above experiment (m.p., 271°) was admixed with the carbazole-2-carboxylic of Plant and Williams[7] (m.p., 276–278°), and the melting point of the mixture was 230–235°. The carbazole-3-carboxylic acid is ruled out, for it melts at 320°. Incidentally, a melting-point determination of a mixture of ethyl carbazole-2-carboxylate (m.p., 165°) and 5-ethylcarbazole-4-carboxylic acid (m.p., 165°) was 145–150°.

Mercuration of 5-ethylcarbazole.—To 19.5 g. (0.1 mole) of 5-ethylcarbazole dissolved in 500 cc. of hot 95% ethanol was added a solution of 31.9 g. (0.1 mole) of mercuric acetate in 500 cc. warm ethanol to which 10 cc. of acetic acid had been added. The mixture was boiled for one and one-half hours, a white crystalline solid separating at the end of one-half hour. After standing for 24 hours, the mixture was filtered and the solid washed with 500 cc. of ethanol. The solid which weighed 13.5 g.* decomposed at 240° with gas evolution but without darkening, and analyzed for 51.7 and 51.4% Hg. When 5.3 g. of the 240° material was extracted with ethanol for 8 hours, the 3.5 g. which remained melted at 242°. This residue, insoluble in the lower alcohols, benzene, acetone and chloroform, analyzed for 53.6, 53.8 and 54.6% Hg. The theoretical value for mercury in 5-ethyl-2,8-diacetoxymercuricarbazole (IV) is 56.3%; and for the bis-(5-ethyl-2-acetoxymercuri-8-carbazyl-) mercury (V) the theoretical percentage of mercury is 54.4.

The alcoholic solution from the mercuration yielded 5-ethyl-2-acetoxymercuricarbazole. This compound was obtained by evaporating the ethanol, and dissolving most of the residue (one g. melting with decomposition at 235° remained) in 600 cc. of warm benzene. The benzene solution yielded 13.8 g. (30.4%) of compound melting at 153°; crystallization from methyl alcohol and benzene raised the melting point to 156°.

Anal. Calc'd for $C_{16}H_{15}NHgO_2$: Hg, 44.2. Found: Hg, 44.7, 44.5.

In a mercuration experiment without solvent, a melt of 0.03 mole of 5-ethylcarbazole and 0.02 mole of mercuric acetate was heated for three hours, and then extracted with 200 cc. of boiling ethanol. The residue (2.9 g.) was the 240°-melting material. To the alcoholic solution was added an excess of an alcoholic solution of calcium chloride in ethanol to give 2 g. of 5-ethyl-2-chloromercuricarbazole, which, after recrystallization from *n*-butyl alcohol, melted at 212° (mixture with known sample), and which gave with iodine and potassium iodide the 5-ethyl-2-iodocarbazole (identified by melting point of mixture with known sample).

5-Ethyl-2-acetoxymercuricarbazole.—The mercurial gave a 75% yield of 5-ethylcarbazole on warming with 10% alcoholic hydrochloric acid.

An 88% yield of 5-ethyl-2-iodocarbazole (m.p. and mixture m.p., 82°) was obtained in the customary manner by treatment with iodine and potassium iodide.

A 93% yield of 5-ethyl-2-chloromercuricarbazole was obtained from the acetoxymercuri compound and calcium chloride. The compound melted at 212–213° after crystallization from *n*-butyl alcohol.

Anal. Calc'd for $C_{14}H_{12}ClHgN$: Hg, 46.6 Found: Hg, 47.1, 47.1.

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*If the reaction is run at a lower temperature and with a lesser volume of ethanol, a greater quantity of the 240° material separates.

A 90% yield of bis-(5-ethylcarbazyl-2-)mercury was obtained from the acetoxymercuri compound and hydrazine hydrate.[6] The bis-mercurial was crystallized from a benzene-petroleum ether mixture and melted at 217°. It was cleaved by alcoholic hydrochloric acid to give 5-ethylcarbazole.

Anal. Calc'd for $C_{28}H_{24}HgN_2$: Hg, 34.1. Found: Hg, 34.4, 34.0.

5-Ethylcarbazole-2-carboxylic acid.—(1) A Schlenk tube containing 0.5 g. of bis-(5-ethylcarbazyl-2-)mercury, 1 g. of lithium shavings and 20 cc. of ether was filled with nitrogen and shaken for 12 hours. Carbonation by solid carbon dioxide gave a 50% yield of 5-ethylcarbazole-2-carboxylic acid, which melted at 226° after crystallization from benzene and ethanol.

Neutralization equivalent: Calc'd, 239; Found, 242.

Anal. Calc'd for $C_{15}H_{13}NO_2$: C, 75.3; H, 5.44; N, 5.86.
Found: C, 75.2; H, 5.40; N, 6.00.

(2) The Grignard reagent of 5-ethyl-2-iodocarbazole (prepared by iodination of 5-ethylcarbazole)[5] was carbonated with solid carbon dioxide to give a 20% yield of 5-ethylcarbazole-2-carboxylic acid. The acid may be sublimed under reduced pressure without decomposition.

(3) 5-Ethylcarbazole (0.075 mole) in acetic acid was brominated by 0.05 mole potassium bromide and 0.056 mole of potassium bromate, to give a 54% yield of pure 5-ethyl-2-bromocarbazole melting at 83° and shown to be identical with the compound obtained by ethylating 2-bromocarbazole.[4] The position of the bromine in the compound prepared by these two procedures is established by the fact that 5-ethyl-2-iodocarbazole (of determined structure) and our bromo compound give 5-ethylcarbazole-2-carboxylic acid *via* carbonation of the respective organometallic compounds.

5-Ethyl-2-bromocarbazole was converted to the corresponding organolithium compound in a customary manner, and the organolithium compound was carbonated by solid carbon dioxide to give a 34% yield of 5-ethylcarbazole-2-carboxylic acid.

(4) Ethyl carbazole-2-carboxylate in acetone was ethylated by means of diethyl sulfate. Hydrolysis of the 5-ethyl ethyl ester gave 5-ethylcarbazole-2-carboxylic acid.

Mixture melting points showed the acids obtained from procedures (1), (2), (3) and (4) to be identical.

5-Ethyl-2,8-diïodocarbazole.—The dimercurial obtained by mercurating 5-ethylcarbazole was treated with iodine and potassium iodide to replace the mercuri groups by iodine. From 10 g. of the dimercurial there was isolated 4 g. of 5-ethyl-2,8-diïodocarbazole which was shown to be identical with the compound obtained by the direct iodination of 5-ethylcarbazole.[5] From the filtrates of the diïodo compound, there was isolated 0.5 g. of 5-ethyl-2-iodocarbazole. No 5-ethyl-triïodocarbazole was isolated.

Dimethyl 5-ethylcarbazole-2,8-dicarboxylate.—A mixture of 3.1 g. of 5-ethyl-2,8-diïodocarbazole, 3 g. of cuprous cyanide, 3 g. of potassium cyanide, 7 cc. of water and 5 cc. of ethanol was heated for 20 hours at 230° in a sealed tube.* The mixture was extracted with sodium hydroxide; the organic acids were precipitated by 15% hydrochloric acid; the precipitate was extracted first with boiling alcohol and then with hot acetic acid; and the residue, which melted above 320°, was ground finely and treated with an excess of diazomethane in ether to give 0.5 g., or a 23%

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* This is in essential accordance with the procedure of ROSENMUND AND STRUCH, *Ber.*, **52B**, 1749 (1919), for the conversion of halides to acids.

yield, of dimethyl 5-ethylcarbazole-2,8-dicarboxylate. The ester melts at 187° after crystallization from benzene-petroleum ether (b.p., 60-68°) and methanol.

Anal. Calc'd for $C_{18}H_{17}NO_4$; C, 69.5; H, 5.47.
Found: C, 69.3; H, 5.55.

Saponification of the ester by 10% potassium hydroxide in 50% ethanol gave 5-ethylcarbazole-2,8-dicarboxylic acid which did not melt at 320°.

Neutralization equivalent: Calc'd, 142; Found, 139.

An authentic specimen of 5-ethylcarbazole-2,8-dicarboxylic acid was synthesized by first ethylating 2,8-diacetylcarbazole and then oxidizing the 5-ethyl-2,8-diacetylcarbazole. The 2,8-diacetylcarbazole in acetone was ethylated by means of diethyl sulfate and sodium hydroxide. The 5-ethyl-2,8-diacetylcarbazole was obtained in 97% yield and melted at 182° after crystallization from methanol and benzene.

Anal. Calc'd for $C_{18}H_{17}NO_2$; C, 77.4; H, 6.09.
Found: C, 77.3; H, 6.05.

To a solution of 150 g. of potassium ferricyanide and 23 g. of potassium hydroxide in 600 cc. of hot water was added 1 g. of 5-ethyl-2,8-diacetylcarbazole. The mixture was refluxed with stirring for one hour and then warmed on a steam bath for 16 hours; cooled; filtered and acidified with 15% hydrochloric acid. Then the acid was again dissolved in alkali, the solution was filtered, and the acid was reprecipitated by hydrochloric acid, after which, it was dried, pulverized and treated with an ether solution of diazomethane. The dimethyl 5-ethylcarbazole-2,8-dicarboxylate obtained in this manner (in 45% yield) melted at 187° after crystallization from methanol, and was shown to be identical with the dimethyl ester obtained from 5-ethyl-2,8-diïodocarbazole.

SUMMARY

Metalation of 5-ethylcarbazole by an organometallic compound like *n*-butyllithium takes place in the 4-position. Mercuration, however, occurs in the 2-position. With dibenzofuran, all varieties of metalating agents so far examined involve the 4-position.

Generalizations are proposed on the metalation of the aromatic nucleus of some related polynuclear types.