molecules thus far prepared the presence of the 1-methylheptyl group had the greatest effect; the compound containing this group is more active than any of the known natural tetrahydrocannabinols.

URBANA, ILLINOIS RECEIVED JULY 9, 1945

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, No. 303]

Condensations by Sodium. XXVIII. The Metalation of Sodium and Potassium Phenoxides

BY AVERY A. MORTON AND ROBERT L. LETSINGER

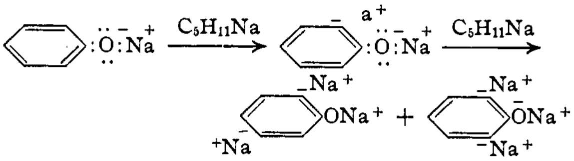
In a previous paper the metalation of benzylsodium by amylsodium was reported. Substitution of the second sodium atom was exclusively in the *meta* position. The orienting influence was attributed to the powerful electron-attracting sodium ion, adjacent to the anion.[1,2] In the present paper a study of the similar metalation of sodium and potassium phenoxide is reported. The object is to observe how much the substitution of an oxygen atom for a methylene group interferes with the *meta* directing influence of the alkali metal cation. The positions taken by the entering sodium ions were determined by carbonation and isolation of the acids.

Salicylic acid, 2-hydroxyisophthalic acid and hydroxyterephthalic acid were found. The first two products are the result of substitution in the *ortho* position but the last can result only from some *meta* substitution. The results of the study show, therefore, that the oxygen atom reduces but does not eliminate the *meta* directing influence of the alkali metal cation, when the conditions are such that the cation is adjacent to the anion.

Meta substitution in the phenoxide ion by an electrophilic reagent[2] is rare. Ingold[3] rates the *ortho-para* directing influence in the phenoxide ion as the most powerful known because the ion has a combined tautomeric and inductive effect. The easy preparations of tribromophenol and picric acid are examples. In such reactions the sodium phenoxide is in a dissociating solvent and the anion can act independently.

In the present experiments the solvent is the non-dissociating dodecane. Hence the phenoxide ion is adjacent to the alkali metal cation and is subject to the strong electron-attracting influence of that agent. The unshared electrons about the oxygen atom will dissipate much of this electron-attracting influence in somewhat the same way that the olefinic electrons screen out the electron-attracting influence of the nitro group in ω-nitrostyrene.[3]

Meta substitution is only partial. Moreover it is found only in the dimetalated product. Probably *ortho* metalation occurs first. The sodium ion attached to the ring can then exert a rear action on the electrons about the oxygen atom and thus weaken the screening effect which the electrons have on the other metal ion. The second substitution then takes place in either the *m*- or *o*-position, as shown.



The potassium ion adjacent to the phenoxide ion exerts a greater effect than does the sodium ion. The metalation by amylsodium is less complete even when the conditions are more strenuous, and the proportion of hydroxyterephthalic acid is 70% greater. These results are in excellent accord with the general behavior of *meta* directing agents in that the stronger the directing force, the slower the rate of substitution and the greater the percentage of *meta* product.

Experimental

Metalation of Sodium Phenoxide.—Phenol (6.2 g., 0.066 mole) was added rapidly at −7° to 15 g. of sodium sand suspended in 250 ml. of dodecane. The apparatus was the high speed stirring assembly used regularly in this work. *n*-Amyl chloride (20.2 g., 0.19 mole) in 30 ml. of dodecane was added dropwise to the cold mixture over a one hour period. The temperature was then raised over a two hour period to 50° at which point the color became gray instead of blue and the mixture became more viscous. The temperature was maintained at this level for one and a half hours, after which the mixture was allowed to cool and subsequently was carbonated. Water was added to remove excess sodium metal, the alkaline layer was extracted with ether, and the aqueous solution of the salts was acidified and then made basic with sodium carbonate. Ether extraction of this solution yielded 0.5 g. of phenol. Reacidification and extraction with petroleum ether and with benzene removed crude salicylic acid and traces of any caproic acid. Ether extraction then removed the mixture of dibasic acids.

The crude salicylic acid (0.6 g.) was purified by washing with petroleum ether and benzene and by recrystallizing successively from water, chloroform and water. When pure it melted at 157.5–159° (cor.) and showed no depression when mixed with an authentic sample.

The total dibasic acid amounted to 1.5 g. A portion (0.739 g.) of this mixture was separated into barium-soluble and -insoluble salts by addition of barium chloride to the ammonium salt solution. From the insoluble barium salt 0.51 g. of acid was isolated; from the soluble barium salt the amount obtained was 0.16 g. The former crystallized in long white needles which melted at 242°. The

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(1) Morton, Little and Strong, THIS JOURNAL, **63**, 1339 (1943).

(2) Morton, *Chem. Rev.*, **35**, 1 (1944).

(3) Ingold, *Ann. Reports*, **23**, 129 (1926); **25**, 137 (1928).

neutralization equivalent was 101 as compared with the value of 100 calculated for the hydrate. The aqueous and alcohol solution had the characteristic blue fluorescence of 2-hydroxyisophthalic acid. Ferric chloride gave a red color. The methyl ester, prepared from methyl alcoholic hydrochloric acid solution, melted at 69.5–70.5° (recorded value[4] 72°).

The acid from the soluble barium salt crystallized from water in a fine white powder. The dried material sublimed at 320–325° (uncor.). Ferric chloride caused a red color. The methyl ester, prepared by use of diazomethane, melted at 91 to 92° after recrystallization from methanol. It was shown to be identical with an authentic specimen of the dimethyl ester of hydroxyterephthalic acid, prepared according to the method of Graebe and Kraft[5] from oxidation of 2,4-dimethylphenol with lead dioxide. The ester was also shown not to be identical with the dimethyl ester of 4-hydroxy-isophthalic acid, prepared from salicylic acid by the method of Tiemann and Reimer.[6] This isomeric ester, which melted at 94–95° (recorded value 96°), when mixed with the dimethyl ester (m. p. 91–92°), derived from the product of metalation, showed a mixed melting point of 73 to 87°.

Metalation of Potassium Phenoxide.—Potassium phenoxide was prepared similarly from 6.2 g. (0.066 mole) of phenol and 2.64 g. (0.066 g. atom) of potassium at −10° in dodecane. Sodium (14 g. or 0.61 g. atom) was then added and converted to sodium sand by the usual method. All processes from this point were the same as before except that the metalation process at 55–60° was continued for five hours because of resistance to metalation. The separation of products yielded 4 g. of caproic acid, 0.29 g. of salicylic acid, 0.17 g. of 2-hydroxyisophthalic acid and 0.12 g. of hydroxyterephthalic acid. A small amount of gummy material was obtained, presumably from pyrolysis[7] of amylsodium. The proportion of hydroxyterephthalic from this preparation was 41% of the total amount of dicarboxylic acids, whereas it was only 24% in the case of the products from sodium phenoxide. Furthermore, the total amount of aromatic acids was less and that of caproic acid, which represents unused amylsodium, was more than in the experiment with sodium phenoxide.

Summary

The metalation of sodium phenoxide and potassium phenoxide by amylsodium has been compared with the previously reported metalation of benzylsodium in order to compare the influence of oxygen with that of methylene on the *meta*-directing effect of the alkali metal cation when adjacent to the phenoxide anion.

The oxygen atom screens out a large amount of the *meta*-directing influence; but one of the demetalated products has the alkali metal cations in the *meta* position.

The influence of the potassium ion is greater than that of the sodium ion, as shown by the quantity of metalation which occurs and the proportion which is in the *meta* position.

CAMBRIDGE, MASSACHUSETTS RECEIVED MARCH 15, 1945

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[4] Graebe and Kraft, *Ber.*, **39**, 800 (1906).

[5] Graebe and Kraft, *ibid.*, **39**, 728 (1906).

[6] Tiemann and Reimer, *ibid.*, **10**, 1562 (1877).

[7] Morton and Newey, THIS JOURNAL, **64**, 2247 (1942).

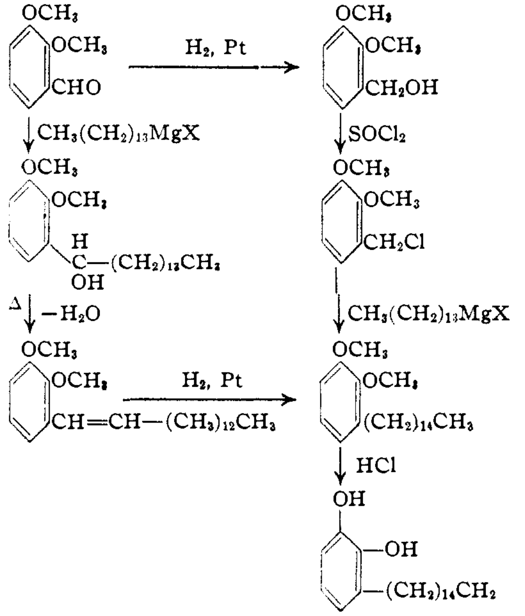
[CONTRIBUTION FROM THE DERMATOSES SECTION, INDUSTRIAL HYGIENE DIVISION, BUREAU OF STATES SERVICES, U. S. PUBLIC HEALTH SERVICE]

The Allergenic Principles of Poison Ivy. V. The Synthesis of 3-*n*-Pentadecylcatechol (Hydrourushiol)[1,2]

BY HOWARD S. MASON

The controversial nature of many recent publications dealing with allergy to poison ivy[3] may be attributed in part to the lack of a standard allergenic substance and to experimentation in its stead with crude, unstandardized and unstable extracts of the irritant plant. This report describes the synthesis in good yield of 3-*n*-pentadecylcatechol, an allergenic solid which has been shown to be present in the irritant oil of plants of the *Rhus* genus.[4] The application of this substance as a *stable, crystalline, standard allergen* to several phases of the poison ivy problem will be reported in subsequent communications.[5]

In the system of syntheses to be described, 3-*n*-pentadecylcatechol was obtained by the hydroly-



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[1] For the fourth article in this series see Mason, THIS JOURNAL, **67**, 1233 (1945).

[2] In accordance with the usage suggested by Landsteiner ("The Specificity of Serological Reactions," revised edition, Harvard University Press, Cambridge, Mass., 1945, p. 204), the title of this series has been changed from "The Toxic Principles of Poison Ivy" to "The Allergenic Principles of Poison Ivy."

[3] Ellis, *J. Allergy*, **14**, 557 (1943).

[4] Majima, *Ber.*, **55**, 172 (1922).

[5] Dunn, Mason and Smith, *J. Inv. Derm.*, in press.