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).

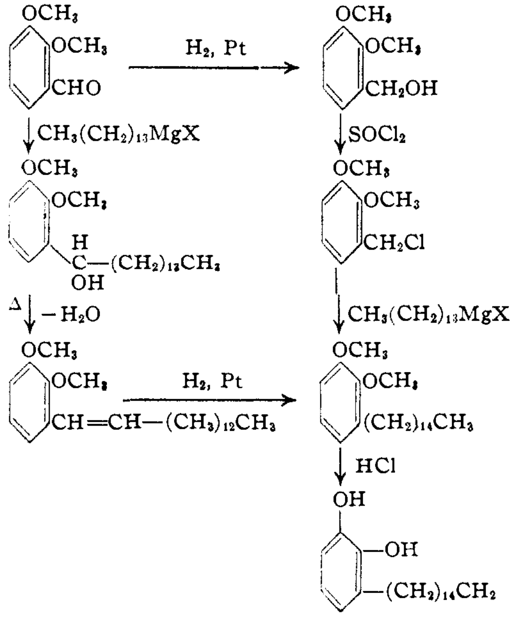
[CONTRIBUTION FROM THE DERMATOSES SECTION, INDUSTRIAL HYGIENE DIVISION, BUREAU OF STATES SERVICES, U. S. PUBLIC HEALTH SERVICE]

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.

sis of its dimethyl ether, which, in turn, was prepared from the accessible 2,3-dimethoxybenzaldehyde.[6] 2,3-Dimethoxy-*n*-pentadecylbenzene had previously been best synthesized in 9% yield[7]; to raise this yield two routes to the substance were systematically investigated. In the first, 2,3-dimethoxybenzaldehyde was catalytically reduced to the corresponding benzyl alcohol in excellent yield. The benzyl chloride which was then prepared from the alcohol was coupled with *n*-tetradecylmagnesium bromide; in addition to a 7% yield of 2,3-dimethoxy-*n*-pentadecylbenzene, this reaction produced octacosane and a substance the analysis of which indicated that it was the product of the coupling of two molecules of 2,3-dimethoxybenzyl chloride. In a parallel reaction with *n*-tetradecylmagnesium chloride a 25% yield of 2,3-dimethoxy-*n*-pentadecylbenzene was obtained. The long chain normal chloride consistently gave better yields and less by-product than the corresponding bromide in this Grignard reaction.

In the second route to 2,3-dimethoxy-*n*-pentadecylbenzene, 2,3-dimethoxybenzaldehyde was treated with either *n*-tetradecylmagnesium bromide or *n*-tetradecylmagnesium chloride. Less by-product was formed in the latter case, and 2,3-dimethoxyphenyl-*n*-tetradecylcarbinol could be isolated in 72% yield. The carbinol was slowly reduced by hydrogen and 5% palladium charcoal to 2,3-dimethoxy-*n*-pentadecylbenzene in 90% yield. The loss of material incident to the isolation and reduction of the carbinol could, however, be avoided by distilling the crude product of the Grignard reaction; 2,3-dimethoxy-*n*-pentadecen-1′-ylbenzene was thus formed and was reduced quantitatively in an Adams reductor. The yield of 2,3-dimethoxy-*n*-pentadecylbenzene prepared in this fashion was 73%.

It has been reported[8] that 2,3-dimethoxy-*n*-pentadecylbenzene may be hydrolyzed to 3-*n*-pentadecylcatechol by heating with hydrobromic acid of specific gravity 1.9 (saturated at 0°). Neither the experimental conditions nor the yield of this reaction were given. Backer and Haack[9] described the splitting of 2,3-dimethoxy-*n*-heptadecylbenzene by heating this ether in a sealed tube with a mixture of acetic acid, hydriodic acid (specific gravity 1.7), phenol and red phosphorus, at a temperature of 180° for ten hours. The yield was reported to be 50%. Both of these methods were repeated several times, but failed to give more than very low yields. In our experience, this failure was due to the formation of a complex mixture of substances which included the monoether, the catechol, a large quantity of polymeric material and *catechol* itself.[10] Since the substances involved are low-melting, and because the soaps of these alkylated phenols tend to form emulsions of considerable stability, the separation of the crystalline 3-*n*-pentadecylcatechol from these mixtures is difficult. Accordingly, a number of reagents for the splitting of phenol ethers were investigated under varying conditions of time and temperature. Of these, only the relatively mild hydrochloric acid, saturated at 0° and acting in a sealed tube at 120–130° for sixty hours proved satisfactory. The recovery of the 3-*n*-pentadecylcatechol formed by this reagent was uncomplicated and the yield amounted to 64%, an over-all yield, based upon the 2,3-dimethoxybenzaldehyde used, of 47%.

Experimental

All melting and boiling points were measured with totally immersed thermometers.

2,3-Dimethoxybenzyl Alcohol.—2,3-Dimethoxybenzaldehyde (Monsanto Chemical Company) was twice distilled; the fraction boiling at 145–147° (24 mm.) was taken for further experimentation. Backer and Haack[6] reported the boiling point of this compound to be 139.5–140° (16 mm.). By reducing the aldehyde at atmospheric pressure with Adams catalyst, 2,3-dimethoxybenzyl alcohol was obtained in high yield. This substance boiled at 155–160° (19 mm.) and melted, after vacuum sublimation, at 45–46°. The phenylurethan melted at 93.5–94.5°. This value has previously been reported[11] to be 94°.

2,3-Dimethoxybenzyl chloride was prepared from the alcohol by treatment with purified thionyl chloride according to the directions of Kaufmann and Müller.[12] The thrice-distilled product boiled at 130–131° (12 mm.).

2,3-Dimethoxy-*n*-pentadecylbenzene: A. From *n*-Tetradecyl Bromide.—*n*-Tetradecylmagnesium bromide was prepared by the procedure described under 2,3-dimethoxyphenyl-*n*-tetradecylcarbinol using 69.3 g. (0.25 mole) of *n*-tetradecyl bromide and 12.2 g. (0.5 mole) of magnesium turnings. The Grignard reagent which formed was transferred from the excess magnesium under nitrogen, and refluxed with 14.9 g. (0.08 mole) of 2,3-dimethoxybenzyl chloride for forty-eight hours. The reaction product was decomposed with ice and hydrochloric acid, extracted with ether, dried and distilled. The fraction boiling above 190° (2 mm.) was dissolved in acetone, in which the solubility of octacosane is low. By successive crystallizations from this solvent, from acetone–alcohol, and finally from alcohol, 10.5 g. (0.027 mole) of octacosane, m. p. 59–60°, 1.0 g. of a compound, m. p. 88–89°, cubic crystals, and 2.0 g. (0.0057 mole, 7.2%) of 2,3-dimethoxy-*n*-pentadecylbenzene were obtained. The latter crystallized in needles and melted at 36.5–37°.

Anal.[13] Calcd. for $C_{23}H_{40}O_2$: C, 79.31; H, 11.57. Found: C, 78.87; H, 11.57.

The compound melting at 88–89° was found to have the same composition as *sym*-di-(2,3-dimethoxyphenyl)-ethane. It was not further investigated.

Anal.[14] Calcd. for $C_{18}H_{22}O_4$: C, 71.6; H, 7.29. Found: C, 71.9; H, 7.47.

B. From *n*-Tetradecyl Chloride.—The coupling of 2,3-dimethoxybenzyl chloride and *n*-tetradecylmagnesium

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[6] This starting material was generously furnished by the Monsanto Chemical Company.

[7] Backer and Haack, *Rec. trav. chim.*, **57**, 225 (1938). See also Majima and Toyama, *Ber.*, **48**, 1606 (1915), and the elegant study in synthesis by Wasserman and Dawson, *J. Org. Chem.*, **8**, 73 (1943).

[8] Majima and Takayama, *Ber.*, **53**, 1907 (1920).

[9] Backer and Haack, *Rec. trav. chim.*, **60**, 656 (1941).

[10] Catechol was also obtained from the corresponding reactions with 2,3-dimethoxybromobenzene (unpublished data). This observation will be amplified in a later paper.

[11] Douetteau, *Bull. soc. chim.*, (4) **11**, 652 (1912).

[12] Kaufmann and Müller, *Ber.*, **51**, 123 (1918).

[13] We are indebted to Mr. E. A. Garlock for this microchemical analysis.

[14] We are indebted to Dr. Arthur T. Ness for this microchemical analysis.

chloride was carried out under the same experimental conditions, and with the same molar proportions as the reaction above. The products were separated in the same manner, and a yield of 25% of 2,3-dimethoxy-*n*-pentadecylbenzene was obtained along with about one-half the amount of octacosane previously found. None of the compound melting at 88-89° could be recovered.

2,3-Dimethoxyphenyl-*n*-tetradecylcarbinol.—Both 2,3-dimethoxybenzaldehyde and *n*-tetradecyl chloride were distilled three times previous to use. The following procedure for the Grignard reaction was *required* for optimal yields: into a three-necked flask were fitted a simple distillation system emptying into the reaction vessel, a mercury-sealed (Hershberg) stirrer, a dropping funnel and an inlet for oxygen-free nitrogen. All ground-glass joints were selected for tightness, and openings were protected with calcium chloride tubes. Magnesium turnings, 2.4 g. (0.1 mole), were placed in the reaction vessel and the whole system was carefully flamed during the passage of dry nitrogen. In a separate flask a small quantity of *n*-tetradecylmagnesium chloride was prepared and dissolved in 200 cc. of sodium-dried ether. Enough ether to cover the magnesium was then distilled from this vessel, and the remainder periodically during the course of the subsequent reaction. The ether in the reaction flask was brought to a gentle reflux over an electric hot-plate and 23.5 g. (0.1 mole) of *n*-tetradecyl chloride *slowly* dripped in over a period of six hours, with constant and vigorous stirring under dry nitrogen. The Grignard reagent began to form immediately; addition of a catalyst for this purpose was unnecessary, and in some early experiments seemed to promote the formation of octacosane. After refluxing the mixture overnight, only traces of magnesium were left and 18.7 g. (0.1 mole) of 2,3-dimethoxybenzaldehyde dissolved in 150 cc. of dry ether was added during the following four hours. The mixture was then further refluxed for eighteen hours. At the end of this period, the reaction vessel was cooled in an ice-salt mixture and a cold aqueous solution containing 0.12 mole of hydrochloric acid slowly added with stirring. The ether layer was then removed, washed and dried. After evaporating the ether, dry, purified petroleum ether b. p. 60-80° was added and the solution cooled. The crystals which formed overnight were filtered off in a cold room at 0°. After recrystallization from methanol, 26.3 g. (0.072 mole, 72%) of 2,3-dimethoxyphenyl-*n*-tetradecylcarbinol m. p. 49-50°, was obtained.

Anal. Calcd. for $C_{23}H_{40}O_3$: C, 75.80; H, 11.06. Found: C, 75.80; H, 11.31.

Reductive Dehydroxylation of 2,3-Dimethoxyphenyl-*n*-tetradecylcarbinol.—Palladinized charcoal was prepared according to the directions of Hartung.[15] 2,3-Dimethoxyphenyl-*n*-tetradecylcarbinol (3.7 g., 0.01 mole) was dissolved in 50 cc. of absolute alcohol; to this mixture was added 5 g. of the catalyst. The mixture took up the theoretical quantity of hydrogen in an Adams reductor in sixteen hours. Upon filtering and cooling, 3.1 g. (0.009 mole, 90%) of a compound which crystallized in needles and melted at 34-35° was recovered. After vacuum sublimation, virtually all of this substance melted at 36.5-37°. A mixed melting point with the compound obtained as described in section A (*vide supra*) showed no depression.

2,3-Dimethoxy-*n*-pentadecen-1′-ylbenzene.—This substance may be prepared by the vacuum distillation of 2,3-dimethoxyphenyl-*n*-tetradecylcarbinol, but for the purposes of preparation it was found unnecessary to isolate the crystalline carbinol. However, certain precautions must be taken to maintain the yield and to obtain a product which may be used directly in the subsequent hydrolysis. At the end of the Grignard reaction, the ether solution is extracted with 60% sodium bisulfite solution to remove unreacted aldehyde; the solution is then dried and the ether removed on a steam-bath. The residual liquid is dissolved in acetone and cooled at 0°. Flaky, lustrous crystals appear after twelve to fifteen hours. This is octacosane, and is filtered off; 3-4 g. is recovered in this manner. The acetone is then evaporated under vacuum and the residue distilled; with the apparatus used in these experiments (a modified Claisen flask) the desired fraction distilled at 234-238° (0.4 mm.), a pale yellow liquid with purple fluorescence. Crystalline 2,3-dimethoxy-*n*-pentadecen-1′-ylbenzene may be isolated by allowing a solution of the distillate in methanol to stand at −10°. Needles are readily formed, m. p. 35-36°.

Anal. Calcd. for $C_{23}H_{38}O_2$: C, 79.77; H, 11.05. Found: C, 79.54; H, 11.33.

2,3-Dimethoxy-*n*-pentadecylbenzene.—The distillate obtained as described above was hydrogenated directly without further purification, using platinum oxide as catalyst, ethanol as solvent, in an Adams reductor. The hydrogenation curve broke sharply at the theoretical point of uptake for one double bond, indicating a high degree of purity of the crude distillate. After filtering the spent catalyst and evaporating the ethanol solution under vacuum, a pale yellow, fluorescent liquid remained. This crystallized very slowly at room temperature, as heavy needles, and could be used directly in the fission reaction. Proceeding in this manner, 0.30 mole of 2,3-dimethoxybenzaldehyde yielded 0.22 mole (73%) of product.

3-*n*-Pentadecylcatechol.—In a heavy-walled Pyrex bomb tube were placed 3.5 g. (0.01 mole) of 2,3-dimethoxy-*n*-pentadecylbenzene and 20 cc. concentrated hydrochloric acid. The tube was cooled in an ice-bath and gaseous hydrogen chloride passed through the aqueous phase until saturation was reached. The tube was sealed and placed in a Carius oven. The time required to reach a temperature of 125° was three-quarters of an hour. The temperature was then maintained at this point for sixty hours.[16] After cooling, the product was dissolved in ether, washed with water, until free of acid, dried over anhydrous sodium sulfate, filtered, and freed of solvent on a steam-bath. The dark red-brown oil which remained was sublimed slowly in high vacuum (0.005 mm.) onto a cold finger. The heavy rhombic crystals which appeared quickly were removed. They melted at 103-104°, and this value was not depressed when they were mixed with catechol. White needles then began to appear on the cold finger; this was 3-*n*-pentadecylcatechol. After exhaustive sublimation 3.1 g. (0.0097 mole) was recovered. It melted at 55-57°. This product was recrystallized from toluene. It then melted at 58-59°. A mixed melting point with 3-*n*-pentadecylcatechol obtained from natural sources showed no depression. The yield was 2.1 g. (0.0064 mole, 64%), and the over-all yield 47% based upon the 2,3-dimethoxybenzaldehyde initially employed.

Addendum.—Since this manuscript was first submitted, it has been found that glacial acetic acid saturated at 0° with hydrogen chloride hydrolyses 2,3-dimethoxy-*n*-pentadecylbenzene more cleanly than the above reagent under the same conditions. The product is obtained by neutralizing the excess acid, extracting with ether, drying the extract, evaporating the solvent and subliming the residue as described above. The crude product is twice crystallized from petroleum ether at 0°; the yield is then 65-70%.

Summary

A procedure for the synthesis of 3-*n*-pentadecylcatechol from 2,3-dimethoxybenzaldehyde in 47% over-all yield is described.

BETHESDA, MARYLAND RECEIVED[17] JUNE 25, 1945

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(15) Hartung, THIS JOURNAL, **50**, 3372 (1928).

(16) Subsequent temperature calibration of the Carius oven indicated a difference between reaction temperature and thermometer reading, which varied under the influence of several factors. Accordingly, the temperatures given above may have been somewhat higher than the actual reaction temperatures. The calibration was carried out by Mr. Theodore D. Perrine.

(17) The manuscript of this article was originally received on October 27, 1944. At the request of informed government officials it was withheld from publication in the interest of national security.—*The Editor*