were analyzed by the gradient density tube method for deuterium. The methanol contained 13.8 atom %, the ketene dimer 12.05 atom % and the methyl acetoacetate 17.48 atom %. These figures correspond to 0.552, 0.482 and 1.398 atoms of deuterium per molecule. The ester recovered was boiled for two hours with 15.5 molar equivalents of methanol. The methanol was distilled away and then the process was repeated with another 14.4 molar equivalents of methanol. The ester was distilled from the flask and analyzed for deuterium: found, 5.04 atom % or 0.403 atom of deuterium per molecule.

ITHACA, N. Y.

[CONTRIBUTION FROM THE WARNER INSTITUTE FOR THERAPEUTIC RESEARCH]

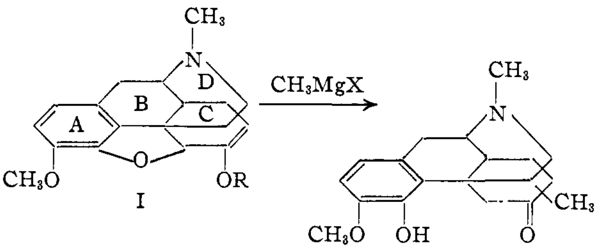
The Mode of Addition of a Grignard Reagent to an Aryl Allyl Ether[1]

BY ROBERT I. MELTZER AND JOHN A. KING

RECEIVED JUNE 23, 1952

By the reaction of phenylmagnesium bromide with *o*-methoxyphenyl crotyl ether it has been shown that a Grignard reagent can cleave an aryl allyl ether by both 1,2- and 1,4-addition.

It was discovered by Small and his co-workers[2] that when a molecule of the codeine type having a double bond in the 6,7-position (I, R = H, $COCH_3$, CH_3) is treated with a methyl Grignard reagent there is produced methyldihydrothebainone (II) in which the 4,5-oxide linkage has been broken and the carbanion from the Grignard reagent has added to the molecule, presumably in the C-ring. Further transformations of II lead to the clinically useful analgesic Metopon. In the hope that the results might give an indication of the structure of methyldihydrothebainone and thus indirectly of Metopon, we undertook an investigation of the direction of addition of a Grignard reagent to an aryl allyl ether.



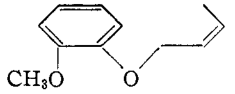
I

II

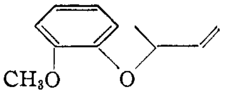
It was shown, a number of years ago, by Luttringhaus and his co-workers[3,4] that phenyl and substituted phenyl allyl ethers (as well as *n*-octyl allyl ether, phenyl allyl thioether and butyl allyl thioether) were readily cleaved by phenyl- and alkylmagnesium bromides at 50–70°, with the carbanion from the Grignard reagent adding to the allyl portion of the ether and formation of a phenol or alcohol from the other portion; in only one case was an ether with a substituted allyl radical used and in this case the hydrocarbon product was not reported, so that no information was available on the direction of the addition. The direction of addition of the Grignard carbanion to the crotyl radical of crotyl mesitoate has been reported,[5] but the mechanism suggested for the Grignard cleavage of allyl esters permits of only one product and is not applicable to allyl ethers. Likewise, results obtained from the Grignard addition to the modified allylic ether butadiene monoxide (3,4-epoxy-1-butene)[6,7] are not translatable to a non-oxidic allyl ether because of two obvious structural differences.[8]

If rings B and D are removed from structure I, and the OR group is replaced by hydrogen, there remains *o*-methoxyphenyl crotyl ether (III), our model substance. That the OR group is not essential to the reaction was evidenced by its occurrence with desoxycodeine-C (I, OR = H).[2]

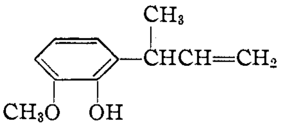
This model compound was obtained as the product of a sequence of reactions designed to give the isomeric substance, *o*-methoxyphenyl methylvinylcarbinyl ether (IV), whose relationship to I is likewise obvious from a comparison of the structures. 1,3-Butyleneglycol was treated with acetyl chloride to yield a product reported[9] to be 3-chlorobutyl acetate. This acetate was saponified to a chloroalcohol which was permitted to react with an ethanolic solution of sodium *o*-methoxy-



III



IV



V

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[1] Presented before the Medicinal Chemistry Section of the XIIth International Congress of Pure and Applied Chemistry, New York, N. Y., September 12, 1951.

[2] L. Small and K. C. Yuen, THIS JOURNAL, **58**, 192 (1936); L. Small, H. M. Fitch and W. E. Smith, *ibid.*, **58**, 1457 (1936); L. Small, S. G. Turnbull and H. M. Fitch, *J. Org. Chem.*, **3**, 204 (1938); L. F. Small and H. M. Fitch (to the Government of the United States), U. S. Patent 2,178,010 (October 31, 1939). See also F. C. Whitmore and A. H. Homeyer (to Mallinckrodt Chemical Works), U. S. Patent 2,510,731 (June 6, 1950); A. H. Homeyer and J. A. Caughlan (to Mallinckrodt Chemical Works), U. S. Patent 2,510,732 (June 6, 1950).

[3] A. Luttringhaus, G. v. Saaf and K. Hanschild, *Ber.*, **71**, 1673 (1938).

[4] A. Luttringhaus, G. v. Saaf, E. Sucker and G. Borth, *Ann.*, **557**, 46 (1947).

[5] R. T. Arnold and R. W. Liggett, THIS JOURNAL, **67**, 337 (1945).

[6] N. G. Gaylord and E. I. Becker, *J. Org. Chem.*, **15**, 305 (1950).

[7] R. W. Freedman and E. I. Becker, *ibid.*, **16**, 1701 (1951).

[8] A possibly more analogous case is the reaction between a Grignard reagent and an α,β-unsaturated acetal or ketal (*e.g.*, F. Straus and M. Ehrenstein, *Ann.*, **442**, 93 (1925)). Since the course of this type of reaction is being investigated by Dr. T. A. Geissman (personal communication) we are not discussing it here.

[9] I. G. Farbenind A.-G., German Patent 524,435 (May 7, 1931).

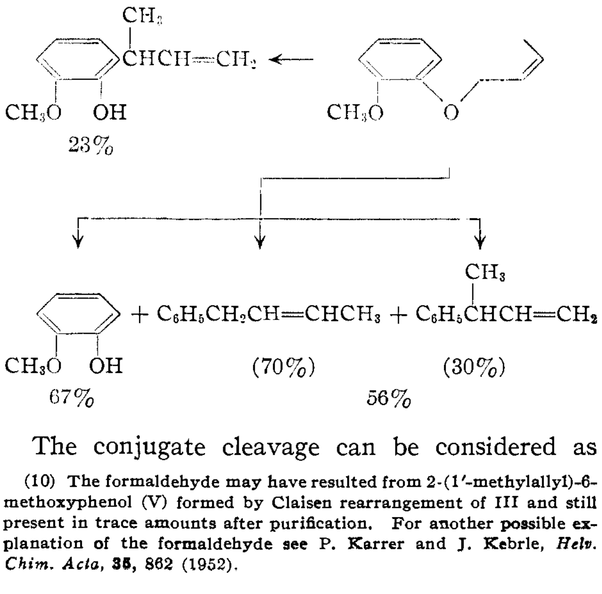
phenoxide to give a 26% yield of what proved to be *o*-methoxyphenyl 3-hydroxybutyl ether. This was converted by thionyl bromide to the corresponding *o*-methoxyphenyl 3-bromobutyl ether which was dehydrohalogenated with alcoholic potassium hydroxide. Because of its importance in our work we decided to prove the structure of the unsaturated ether rather than rely upon its method of synthesis as a proof of structure. Neutral permanganate oxidation yielded *o*-methoxyphenoxyacetic acid instead of the expected α-(*o*-methoxyphenoxy)-propionic acid, this being the first indication that we had structure III instead of the expected IV. The olefinic ether III on catalytic reduction took up one mole of hydrogen and gave *o*-methoxyphenyl *n*-butyl ether and on ozonolysis produced much acetaldehyde but only a trace of formaldehyde.[10] Either the initial reaction with 1,3-butyleneglycol produced at least some 4-chloro-2-butyl acetate or a rearrangement occurred in one of the subsequent steps. We are investigating these possibilities.

The reaction of III with phenylmagnesium bromide furnished three principal products. One of these was the cryptophenol V, formed in 23% yield by Claisen rearrangement of III; the material had the empirical formula $C_{11}H_{14}O_2$, it gave a good yield of formaldehyde on ozonolysis, and vigorous alkaline permanganate oxidation of its methyl ether gave 2,3-dimethoxybenzoic acid.

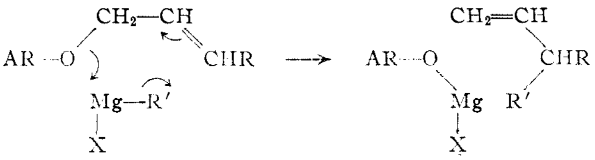
The major cleavage product was the expected guaiacol, obtained in 67% yield; this plus the 23% yield of V thus accounted for 90% of the aromatic portion of the starting material.

The other cleavage product, from addition of the Grignard carbanion to the crotyl portion of the ether, was isolated in 56% yield. This material gave both acetaldehyde and formaldehyde on ozonolysis and quantitative infrared analysis of its hydrogenation product showed the latter to consist of a mixture of 70.2 ± 1.1% *n*-butylbenzene and 29.8 ± 0.7% *s*-butylbenzene.

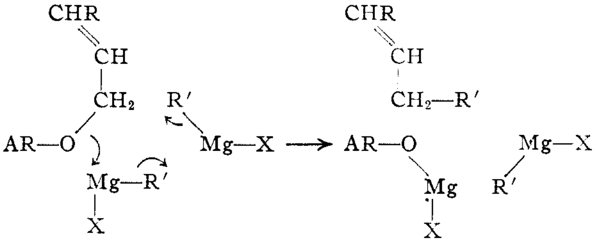
One is therefore able to portray the over-all reaction in the manner



The conjugate cleavage can be considered as



proceeding *via* a cyclic transition state[11] while the direct cleavage can be considered to occur analogously to the addition of Grignard reagents to ketones as was recently demonstrated by Swain and Boyles.[12]



Because we observed both modes of addition of the Grignard carbanion to our model substance no conclusions can be drawn, from our work, concerning the structure of methyldihydrothebainone.

Acknowledgment.—We wish to acknowledge the technical assistance of Mr. J. P. Harang.

Experimental[13,14]

3-Chlorobutanol.[9]—Acetyl chloride (955 g., 12.15 moles) was added to a mixture of 1,3-butylene glycol (900 g., 10 moles) and anhydrous calcium chloride (206 g., 1.89 moles) during 0.5 hour while the temperature of the reaction mixture was maintained below 10°. The stirred reaction mixture was then allowed to warm to room temperature, held there for 20 hours, then heated to 50° and held there for one hour. It was then cooled and poured on to 1500 g. of ice. The layers were separated and the aqueous layer was extracted twice with 100-cc. portions of ether. The organic layer to which had been added the ethereal extracts was washed first with 20% sodium chloride solution and then with 20% sodium carbonate solution and after being dried over magnesium sulfate was distilled to give 1074 g. of material, b.p. 60–76° (13 mm.). The reported boiling point is 71° (13 mm.). Our material was considered sufficiently pure for submission to ester interchange without additional fractionation. The entire lot of 1074 g. was refluxed for 50 hours with 2.5 l., of methanol and 2.5 ml. of concentrated hydrochloric acid under a two-foot Fenske fractionating column which permitted removal of the methyl acetate-methanol azeotrope. The column was operated with intermittent take-off, with the volume of the still pot content being maintained constant by the addition of more methanol. Fractional distillation of the reaction mixture gave 784 g. (73% yield) of product boiling at 66–68° (15 mm.) and having $n^{27}\mathrm{D}$ 1.4396. The reported[9] boiling point is 61° (10 mm.).

***o*-Methoxyphenyl 3-Hydroxybutyl Ether.**—To a solution of sodium (76 g., 3.3 moles) in absolute ethanol (1500 cc.) there was added a solution of guaiacol (446 g., 3.15 moles) n absolute ethanol (750 cc.) followed by a solution of 3-

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(10) The formaldehyde may have resulted from 2-(1'-methylallyl)-6-methoxyphenol (V) formed by Claisen rearrangement of III and still present in trace amounts after purification. For another possible explanation of the formaldehyde see P. Karrer and J. Kebrle, *Helv. Chim. Acta*, **35**, 862 (1952).

(11) There is obviously no steric disinclination toward formation of such a cyclic transition state by non-cyclic allylic ethers and a study of molecular models of the codeine type (I), in which ring C is in back of and at about a right angle to the plane of rings A and B, leads us to believe that such a transition state is not impossible with the codeine type allylic ether although attack of RMgX from in front of the plane of rings A and B to give direct cleavage appears to be easier. Our conclusions are not necessarily at variance with those of E. R. Alexander and G. R. Coraor, THIS JOURNAL, **73**, 2721 (1951), who believe that a complex of this type cannot be formed with 2-cyclohexenone.

(12) C. G. Swain and H. B. Boyles, *ibid.*, **73**, 870 (1951).

(13) Microanalyses and ultraviolet spectral measurements were carried out in these laboratories under the supervision of Dr. F. A. Buhler.

(14) Melting points and boiling points are uncorrected.

chlorobutanol (323 g., 3.0 moles) in absolute ethanol (300 cc.). The reaction mixture was refluxed 4 hours, the sodium chloride was removed by filtration, and the solvent was removed from the filtrate under vacuum. The residue was taken up in ether and washed successively with four 150-cc. portions of 5% sodium hydroxide, with 100 cc. of 4 *N* hydrochloric acid and with 50 cc. of water. The layers tended to emulsify and separations were slow. The ethereal solution was dried over magnesium sulfate and then fractionally distilled through an eight-inch Vigreux column, the portion boiling in the range 115–130° (1 mm.) being arbitrarily divided into five successive fractions. On storage in the refrigerator the early fractions gave small amounts of solid material while the latter fractions gave considerable amounts of solid. Each of the fractions was slurried with ligroin (b.p. 28–38°) and then filtered. The five filtrates were combined, redistilled, and the separation process was repeated. All of the solid fractions were combined and recrystallized from a mixture of ligroin (b.p. 60–68°) and a little ethanol. The average yield of product, m.p. 46–47°, obtained in six experiments was 26%.

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.21. Found: C, 67.28; H, 8.17.

o-**Methoxyphenyl 3-Bromobutyl Ether.**—To a stirred solution of *o*-methoxyphenyl 3-hydroxybutyl ether (307.7 g., 1.57 moles) in a mixture of dry benzene (1600 cc.) and dry pyridine (150 cc.) there was added thionyl bromide (356 g., 1.72 moles) while the temperature of the mixture was maintained below 20°. The reaction mixture was then stirred three hours at room temperature, an additional 150 cc. of pyridine was added, stirring was continued for one hour at room temperature and the mixture was then heated to refluxing and held there for three hours. At the end of this time, the reaction mixture was chilled, diluted with 250 cc. of dry ether, allowed to settle, and the supernatant was decanted from the precipitated pyridine hydrobromide. The decanted solution was washed twice with 100-cc. portions of water, the aqueous washings being combined and used to dissolve the originally precipitated hydrobromide. This aqueous solution was then extracted four times with 50-cc. portions of ether, the ethereal extracts being added to the original reaction solution. After being dried over magnesium sulfate this combined solution was fractionally distilled. The product boiled in the range of 129–138° (0.5 mm.) and was redistilled rapidly through a 3-ball Snyder column or a short Vigreux column to give 40–45% average yields of material boiling with some decomposition at 116–118° (0.65 mm.). Because of the decomposition accompanying distillation, satisfactory analyses on the product could not be obtained.

o-**Methoxyphenyl Crotyl Ether** (III).—To a warm solution of potassium hydroxide (357 g., 6.43 moles) in absolute ethanol (1200 cc.) there was added *o*-methoxyphenyl 3-bromobutyl ether (91.3 g., 0.352 mole). After the solution had been stirred for 30 minutes it was stirred under reflux for an additional one-half hour and then cooled and filtered. The filtrate was concentrated under vacuum at a bath temperature of not over 50° until solid material began to separate. The mixture was then diluted with four volumes of water and extracted with ether, the combined ethereal extracts were dried over magnesium sulfate and fractionally distilled to give average yields of 70–85% of product boiling at 76–77° (0.5 mm.) or 56–57° (0.2 mm.) and having $n^{25}D$ 1.5299.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.14; H, 7.92. Found: C, 74.10; H, 8.04.

The product was insoluble in 5 *N* sodium hydroxide, gave a negative ferric chloride test and only a very weak Folin–Ciocalteau phenol test; after the material had been refluxed at atmospheric pressure for five minutes its solubility in 5 *N* sodium hydroxide was still not appreciable but it gave a red coloration with ferric chloride and an immediate strong positive phenol test with Folin–Ciocalteau reagent.

Oxidation of III to *o*-**Methoxyphenoxyacetic Acid.**—To a stirred solution of 10 g. of the aryl crotyl ether in 400 cc. of alcohol there was added dropwise during 20 minutes 300 cc. of 5% aqueous potassium permanganate while the temperature of the reaction mixture was maintained at 15°. The precipitated MnO_2 was removed by filtration, washed with alcohol and the washings combined with the filtrate. The combined solution was concentrated to 200 cc. (the concentrate was alkaline) and extracted with ether, the extract being discarded. The extracted solution was then acidified to *p*H 2 with concentrated hydrochloric acid and re-extracted with ether to remove the acidic oxidation product. The ethereal extract was dried over magnesium sulfate and then evaporated to dryness to leave 4 g. of residue which, after recrystallization from a mixture of carbon tetrachloride and benzene, melted at 119–120°. Because the reported[15] melting point of the α-(2-methoxyphenoxy)-propionic acid which we had been expecting was 85° we had our compound analyzed and found that it checked for the next lower homolog.

Anal. Calcd. for $C_9H_{10}O_4$: neut. equiv., 182; C, 59.33; H, 5.55. Found: neut. equiv., 177; C, 59.85; H, 5.57.

Since the melting point reported[16] for *o*-methoxyphenoxyacetic acid is 121° and our compound melted at 119-120° and was in agreement with the empirical formula of the phenoxyacetic acid, we considered their identity established.

Hydrogenation of III to *o*-**Methoxyphenyl Butyl Ether.**—A solution of III (3.55 g., 0.02 mole) in absolute alcohol (25 cc.) absorbed 0.02 mole of hydrogen at room temperature and 3 atmospheres pressure in the presence of 0.20 g. of platinum oxide. The product was identified as the normal butyl ether of anisole by its conversion to the 4,5-dinitro derivative, melting point and mixed melting point with authentic sample[17] 89–91°.

Ozonolysis of III.—Quantitative determination of the amounts of formaldehyde obtained in the several ozonolyses was by our own modification of the procedure described by Doeuvre.[18] Solvents and reagents were prepared in the following manner:

Sulfur dioxide was passed through a solution of 4 g. of basic Fuchsin in 2 l. of distilled water for three hours. The amber solution was then placed under water-pump vacuum for 2.5 hours after which it was filtered through fluted filter paper.

Ethyl acetate was refluxed over phosphorus pentoxide and then filtered and distilled.

Two liters of glacial acetic acid was refluxed over 30 g. of chromic acid for one-half hour and then distilled. The ethyl acetate and acetic acid were mixed in the proportions of 3:2 and this solution was used as the solvent for the ozonolyses.

Concentrated hydrochloric acid was diluted with distilled water in a ratio of 10:7.

The exact concentration of formaldehyde in 37% U.S.P. formaldehyde solution was determined by the method of U.S.P. XIII. This was then carefully diluted just prior to use to a solution containing 0.0420 mole/ml. An attempt to use a formaldehyde solution of about 0.002 mole/ml. gave poor color formation.

A working curve was made as follows: to each of six 100 ml. volumetric flasks was added 50.0 ml. of fuchsin reagent, 25.0 ml. of hydrochloric acid solution and 2.0 ml. of ethyl acetate–acetic acid solution. Diluted formaldehyde solution was then added. To one flask 4.0 ml. was added, to the second 8.0 ml., to the third 12.0 ml., to the fourth 16.0 ml., to the fifth 20.0 ml., and to the last none. Each flask was diluted to mark with distilled water and allowed to stand for 5 hours. At the end of this time 4 ml. was diluted to 100.0 ml. with water and readings were taken on a Lumetron colorimeter, Model No. 402E using an N-490 filter. The plot of these values was the working curve and did not deviate significantly from a straight line on a semi-log scale.

In practice, some of these knowns were run at the same time as the unknowns as a check on the reagents and work.

When the unknowns were run, 2.0 ml. of the ozonolysis reaction solution was used in place of the formaldehyde and ethyl acetate–acetic acid solutions above. Unknown samples were run in duplicate and checked one another to within 2%.

As a standard substance upon which to do an ozonolysis we selected eugenol since it should give one mole of formaldehyde per mole of olefin. Ozonolyses were performed with 4 to 5% ozone in oxygen at a total flow rate of approximately 9.0 liters per hour. A solution of 1.613 g. of distilled eugenol in 100 ml. of ethyl acetate–acetic acid was submitted to ozonolysis at −20° until the effluent gas turned potas-

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(15) C. A. Bischoff, *Ber.*, **33**, 1392 (1900).

(16) K. Auwers and K. Haymann, *ibid.*, **27**, 2795 (1894).

(17) J. Allen and R. Robinson, *J. Chem. Soc.*, 376 (1926).

(18) J. Doeuvre, *Bull. soc. chim. France*, [5] **3**, 612 (1936); [4] **45**, 146 (1929).

sium iodide solution dark yellow. The color change was not sharp and the reaction required 75 minutes. The contents of the reaction chamber were quantitatively transferred to a 100-ml. volumetric flask, diluted to mark with solvent and 2.0 ml. very quickly removed using a pipet. This showed 81% of the theoretical formaldehyde.

By exactly the same procedure 1.763 g. of *o*-methoxyphenyl crotyl ether (III), ozonized three-quarters of an hour, yielded only a trace of formaldehyde. The solvent itself on ozonolysis yielded no formaldehyde.

The remainder of the ozonolysis solutions was used to prepare dimedon derivatives of the volatile aldehydes. The solutions were added to a refluxing mixture of 3 g. of zinc dust, 60 ml. of water and about 25 mg. each of silver nitrate and hydroquinone. After being refluxed for 1 hour, the reaction mixture was distilled down to a volume of about 30 ml., the distillate being led into a series of three wash bottles, each containing about 25 ml. of water. The contents of the three wash bottles were combined, 2 g. of dimedon was added, and the *p*H was adjusted to 4.6 with sodium hydroxide. The mixture was stirred for 12 hours, then the ethyl acetate layer was distilled off and the residue was allowed to stand in the cold for several hours. The solutions were then filtered and the precipitates recrystallized from aqueous methanol.

The dimedon derivative of formaldehyde was obtained from eugenol but not from *o*-methoxyphenyl crotyl ether (III); the latter substance formed only the dimedon derivative of acetaldehyde.

Reaction of Phenylmagnesium Bromide with *o*-Methoxyphenyl Crotyl Ether (III).—To a solution of phenylmagnesium bromide prepared from bromobenzene (33 g., 0.21 mole) and magnesium (5.5 g., 0.226 mole) in anhydrous ether (125 cc.) there was added during 10 minutes a solution of *o*-methoxyphenyl crotyl ether (34.2 g., 0.192 mole) and anhydrous ether (40 cc.). The reaction was exothermic and the reaction mixture turned brown. After the addition was complete the mixture was maintained at reflux by the application of external heat. After 20 minutes refluxing, a white precipitate formed but the appearance of the mixture did not otherwise change during the 6.5 hours of refluxing. After this time 150 cc. of 4 *N* hydrochloric acid was added and the mixture was stirred a number of hours until it was clear and would separate into two clear layers. The organic layer was separated and washed successively four times with 4 *N* sodium hydroxide, twice with 1 *N* sodium hydroxide, twice with water, once with 4 *N* hydrochloric acid and then dried over magnesium sulfate.

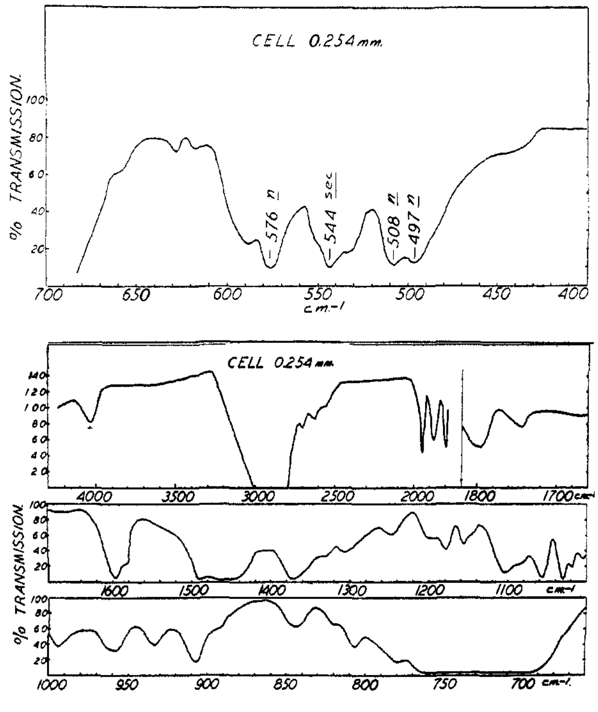

Fig. 1.—Infrared spectrum of an undiluted sample of butylbenzenes.

Fractional distillation of the solution gave 14.2 g. of product boiling at 70–75° (17 mm.), n^{23}D 1.5095; 7.3 g. of material boiling at 131–140° (17 mm.), n^{23}D 1.5469; and 1 g. of residue. Redistillation of the first fraction (butenylbenzene) gave 0.25 g. of forerun, 12.35 g. of distillate, b.p. 70–76° (20 mm.), n^{25}D 1.5081, and a residue of 0.75 g.

Anal. Calcd. for $C_{10}H_{12}$: C, 90.85; H, 9.15. Found: C, 90.77; H, 9.10.

Fractional redistillation of a 6.6-g. sample through a 4″ wire screen column with fractions arbitrarily taken over 2° boiling ranges between 70 and 76° at 20 mm. pressure gave three approximately equal portions with n^{24}D 1.5071, 1.5082 and 1.5092. The found analysis on these respective samples were: C, 90.75; H, 9.50; C, 91.16; H, 9.23; C, 90.73, H, 9.41. The maximum molecular extinction coefficient of all these samples in 95% ethanol at concentration of about 250 mg./l. was at 260 mμ and had the following values, respectively; 250, 247 and 274. The minimum molecular extinction coefficient at 234 mμ had the following respective values: 94, 88 and 74.

These values were not in agreement with the high absorption of a double bond in conjugation with the benzene ring as in styrene ($\lambda_{max.}$ 245 mμ),[19] but was in agreement with the low maximum absorption shown by allylbenzene ($\lambda_{max.}$ 263 mμ[20]).

Ozonolysis of the material as described gave both acetaldehyde and formaldehyde, isolated as their dimedon derivatives, and determination of the formaldehyde by the colorimetric method which revealed 81% of the methylene group of eugenol showed there to be 24% of a methylene group present. This result is in satisfactory agreement with the results obtained by quantitative infrared spectral analysis of the hydrogenated butenylbenzene.

A 3.0-g. sample of butenylbenzene in 75 ml. of ethanol took up the expected amount of hydrogen in the presence of Raney nickel in 1.5 hours.

The infrared[21] absorption spectrum of an undiluted sample of the butylbenzene (Fig. 1) confirmed the identity of the material as a mixture of butylbenzenes, the curve being a composite of those of *n*- and *s*-butylbenzene.[22]

A Perkin-Elmer Model 12B infrared spectrometer was used for spectral measurements. The bands at 497, 508 and 576 cm.$^{-1}$ were used for the quantitative determination of the normal compound and the band at 544 cm.$^{-1}$ for the secondary compounds. Five standard solutions of varying known relative proportions of *n*- and *s*-butylbenzene in carbon tetrachloride solution were prepared and a plot of concentration *vs.* transmission at the selected frequencies showed close adherence to Beer's law; from the corresponding data obtained on a solution of our butylbenzene in carbon tetrachloride its percentage composition was determined. The amounts of *n*- and *s*-butylbenzene in the sample were shown to be 70.2 ± 1.1% and 29.8 ± 0.7%, respectively.

The high-boiling (7.3 g.) fraction obtained in the fractional distillation of the ethereal layer of the original reaction mixture was treated with 4 *N* sodium hydroxide whereupon there separated 1.6 g. of diphenyl identified after recrystallization by its melting point of 68–68.5° alone or mixed with an authentic sample and by the melting point of its derivative 4′-phenylbenzophenone-2-carboxylic acid, m.p. 222–223° alone or mixed with authentic[23] sample.

The sodium hydroxide solution obtained on removal of the diphenyl became oily on dilution. The solution was acidified and extracted with ether. Evaporation of the ether gave an oil which although soluble in 4 *N* sodium hydroxide could be extracted completely by ether. The ether layer was dried, filtered and evaporated. Over 5 g. of oil was recovered. This was distilled, b.p. 135–137° (2 mm.),

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(19) B. Arends, *Ber.*, **64**, 1936 (1931).

(20) Mme. Ramart-Lucas and P. Amagat, *Bull. soc. chim. France*, **51**, 108 (1932).

(21) The infrared spectral measurements and the interpretation of the results were made by Dr. Robert L. Bohon, in The Anderson Physical Laboratory, Champaign, Illinois.

(22) American Petroleum Institute–National Bureau of Standards Project 44 Catalogue of Infrared and Ultraviolet Spectrograms Nos. 468, 470, 486 and 487.

(23) H. W. Underwood and W. L. Walsh, THIS JOURNAL, **57**, 940 (1935).

n^{27}D 1.5315. Analysis was acceptable for 2-(1′-methylallyl)-6-methoxyphenol.

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.13; H, 7.92. Found: C, 74.39; H, 8.17.

This material gives a ferric chloride phenol test and decolorized permanganate readily.

A solution of 0.6 g. of this phenol and 1.2 g. of 3,5-dinitrobenzoyl chloride in 10 ml. of pyridine was kept at reflux for 5 hours, cooled and poured into 200 ml. of cold 5% sulfuric acid. The resulting oil was taken up in ether and washed with water, 5% sodium hydroxide and then with water. Evaporation of the dried ether gave a semi-solid. Recrystallization from ethanol gave a solid, m.p. 127–128°. This analyzed correctly for the 3,5-dinitrobenzoate of 2-(1′-methylallyl)-6-methoxyphenol.

Anal. Calcd. for $C_{12}H_{10}N_2O_7$: C, 58.06; H, 4.33. Found: C, 57.90; H, 4.37.

Ozonolysis for 15 minutes of 0.682 g. of the phenol showed 78% of the expected methylene group using the above described method which showed 81% of the methylene group of eugenol.

A solution of 0.75 g. of the phenol in 5 ml. of 20% sodium hydroxide was stirred vigorously with 15 ml. of dimethyl sulfate for 25 minutes. An additional 1.5 ml. of dimethyl sulfate and 5 ml. of 50% sodium hydroxide was added and stirring was continued for 2 hours. After heating gently a few minutes, the reaction mixture was extracted with ether. The ether, after drying, left 0.75 g. of residual oil. This was shaken with 20 ml. of 20° sodium hydroxide and 4.5 g. of potassium permanganate in 50 ml. of hot water. The solution turned green. The reaction mixture was filtered. The filtrate, which still had MnO_2 in it, was acidified and extracted with ether. The dried ether on evaporation left 0.3 g. of residue. This was taken up in 4 *N* sodium hydroxide and washed with ether. Acidification, extraction with ether and evaporation of the ether left a solid which was recrystallized from water with the aid of Darco G-60. The product melted at 120–120.5°. The melting point of *o*-veratric acid is reported as 122°.[24]

The alkaline and water washings of the ether solution of the original reaction mixture were combined, acidified, extracted with ether, and the ether layer dried over magnesium sulfate. Fractional distillation gave 16.2 g., n^{23}D 1.5429, distilling at 93° (17 mm.), 2.2 g., n^{23}D 1.5350, distilling at 110–135° (17 mm.) and 1 g. of residue.

The refractive index of the first fraction compared well with that of our guaiacol, n^{24}D 1.5426. The 3,5-dinitrobenzoate prepared according to Phillips and Keenan[25] melted at 135–136° and did not depress the melting point of an authentic sample. The picrate melted at 86–88° as did the picrate of authentic guaiacol.

The second fraction gave a 3,5-dinitrobenzoate which did not depress the melting point of the 3,5-dinitrobenzoate obtained from the fraction identified as 2-(1′-methylallyl)-6-methoxyphenol.

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Syntheses in the 5,8-Dihydroxyquinaldine Series

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A number of 5,8-dimethoxyquinaldine derivatives have been synthesized from 2,6-nitro- and amino-substituted derivatives of hydroquinone dimethyl ether. Some aspects of their reactions have been studied, and 4-(β-diethylaminoethylamino)-5,8-dihydroxyquinaldine has been prepared for biological tests.

Only few derivatives of 5,8-dihydroxyquinoline have become known which contain functional groups associated with special physiological properties. For example, no dialkylaminoalkylaminoquinoline carrying hydroxyl groups in positions 5 and 8 has been described, in spite of the possible significance of such substitutions for the Schönhöfer theory of antimalarial action of aminoquinolines.[1] This study contributes to the chemistry of compounds in this series.

As starting materials for our syntheses, 2,6-dinitrohydroquinone (I)[2] was prepared in excellent yield from its 4-monoacetate (II)[3] by acid-catalyzed methanolysis. It was methylated with diazomethane in ether–methanol solution; the resulting 1,4-dimethoxy-2,6-dinitrobenzene (m.p. 109–111°) (III) proved to be different from the 2,3-dinitro isomer (m.p. 177°) or the 2,5-dinitro isomer (m.p. 202°).[4] One of the two nitro groups of III was reduced selectively with stannous chloride in ethanolic hydrogen chloride; the widely used monoreduction of dinitrobenzene derivatives with ammonium sulfide[5] was not applicable to this case because of the instability of III in alkaline medium. In addition to 2,5-dimethoxy-3-nitroaniline (IV), a small amount of an *x*-chloro-2,5-dimethoxy-3-nitroaniline was obtained as a by-product in the stannous chloride reduction.

The amine (IV) was acetylated with acetic anhydride in the presence of triethylamine and the 2,5-dimethoxy-3-nitroacetanilide (V) was hydrogenated to 3-acetamido-2,5-dimethoxyaniline (VI). We were unable to convert IV to 2,5-dimethoxy-3-nitrophenol by the diazo reaction, perhaps because of the mobility of the methoxyl group in this series[6] or of the enhanced coupling ability of *m*-alkoxy substituted phenols.[7] Even the diazotization of 2,5-dimethoxyaniline carried out as a simplified model experiment gave only a 25% yield of 2,5-dimethoxyphenol.[8]

3-Acetamido-2,5-dimethoxyaniline (VI) was condensed with ethyl acetoacetate and the resulting β-(2,5-dimethoxy-3-acetamidoanilino)-crotonate was cyclized to 4-hydroxy-5,8-dimethoxy-7-acetamidoquinaldine (VII) in boiling diphenyl ether. Neither

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[4] R. Nietzki and F. Rechberg, *Ber.*, **23**, 1211 (1890).

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[8] 2,5-Dimethoxyphenol had been prepared previously only by the equivocal reduction of apione or dibromoapione with sodium and alcohol [G. Ciamician and P. Silber, *Ber.*, **24**, 2608 (1891)].