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ADDITION OF PHENOLS TO THE ETHYLENIC LINKAGE.¹ REACTION MECHANISM AND SYNTHESIS OF CERTAIN PHENOLIC ETHERS

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RECEIVED OCTOBER 25, 1930

PUBLISHED JANUARY 12, 1931

Theoretical Part

Isolated cases of reactions between phenols and unsaturated compounds have been reported before. Isoprene,² cinnamic acid,³ cyclohexene,⁴ isoamylene, styrene⁵ and acetylene⁶ have been condensed with phenol type compounds under the influence of mineral acid with the formation of the corresponding substituted phenol in most cases.

In 1925 Niederl⁷ showed that acetone condenses with phenols and that the resulting compounds could also be obtained by the interaction of unsaturated ketones with phenols. The reaction was shown to be an addition of the phenol to the unsaturated ketone.⁸ This reaction was then systematically studied and it was found that the following types of unsaturated compounds would condense with phenols: alcohols,⁹ ethers,¹⁰ esters,¹¹ aldehydes,¹² ketones,¹³ acids,¹⁴ nitriles, amines, halides and ethylene oxide.¹⁵

The purpose of the present research was to continue the work on into the unsaturated hydrocarbon series in order to study the products obtained

¹ Constructed from part of the thesis presented by Samuel Natelson to the Faculty of the Graduate School of New York University in candidacy for the degree of Doctor of Philosophy, 1931. This research was presented at the Cincinnati meeting of the American Chemical Society.

² Claisen, German Patent 374,142 (1923).

³ Liebermann and Hartmann, *Ber.*, **24**, 2582 (1891); **25**, 957 (1892).

⁴ Schrauth and Quasebarth, *ibid.*, **57**, 854 (1924).

⁵ König, *ibid.*, **24**, 3889 (1891).

⁶ Wenzke and Nieuwland, *THIS JOURNAL*, **46**, 177 (1924).

⁷ Niederl, "Inaugural Dissertation," University of Graz, Austria, April, 1925; compare Jordan, Schering-Kahlbaum, British Patents 279,855, 279,857, 280,924 (1928); Canadian Patents 281,114, 281,120 (1928).

⁸ Niederl, *THIS JOURNAL*, **50**, 2230 (1928); Niederl and Casty, *Monatsh.*, **51**, 1038 (1929).

⁹ Niederl and McGreal, Columbus Meeting, American Chemical Society, 1929.

¹⁰ Storch, Sc.M. Thesis, New York University, 1930.

¹¹ Adams, Sc.M. Thesis, New York University, 1930.

¹² Niederl, Smith and Wilson, Columbus Meeting, American Chemical Society, 1929.

¹³ Niederl, *THIS JOURNAL*, **51**, 2426 (1929); Knowles, Sc.M. Thesis, New York University, 1929; Sen and Quadrat-I-Khuda, *J. Indian Chem. Soc.*, **7**, 167 (1930).

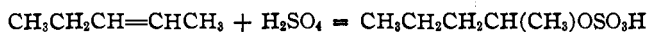
¹⁴ Liebermann and Hartmann, *Ber.*, **24**, 2582 (1891); **25**, 957 (1892).

¹⁵ Work is now in progress at New York University.

with a view toward a probable mechanism for all these condensation reactions with phenols.

β -Amylene and di-isobutylene were treated with phenol and the cresols in the presence of sulfuric acid. The corresponding ethers were obtained. The following mechanism is offered for this reaction, taking the reaction between β -amylenes and *m*-cresol as an example.

It is first assumed that sulfuric acid is added to the unsaturation of amylenes.¹⁶ An ester would be formed of the structure



Since condensation took place, it could only have taken place in one of two ways: either in the formation of a five carbon substituted phenol, or in an elimination of sulfuric acid with the formation of an amyl cresyl ether $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)\text{OSO}_3\text{H} + \text{H} \text{OC}_6\text{H}_4(\text{CH}_3) = \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)\text{OC}_6\text{H}_4(\text{CH}_3)$

This ether had not been reported in the literature up to this time and the proof of its structure was therefore undertaken. It was synthesized according to the Williamson method.¹⁷ The resulting compound was shown to be identical with the ether obtained using the condensation method.

It appears from the work accomplished that the condensation of unsaturated ketones, alcohols, ethers, esters, aldehydes, acids and hydrocarbons (where the reactions are carried out at higher temperatures) takes a different course than the condensation of unsaturated hydrocarbons with phenols in the cold, substituted phenols being obtained in the first case and ethers in the latter. An explanation was then sought which would harmonize these differences. Claisen¹⁸ and others¹⁹ have shown that alkyl phenyl ethers with a negative group in the alkyl radical are prone to rearrange upon heating or, more rapidly, in the presence of mineral acid or zinc chloride. The formation of substituted phenols upon condensation of unsaturated alcohols, ethers, esters, aldehydes, ketones and acids with phenols can now be better explained. Addition of sulfuric acid is first assumed and then elimination of the acid with the formation of an ether. Ethers of these types, as mentioned above, have been shown to rearrange rapidly, especially in the presence of mineral acids. Under the conditions of the experiment, therefore, the ether was not isolated, but the substituted phenol was obtained.

In the condensation of amylenes and di-isobutylene with phenols in the cold, ethers were formed with a saturated alkyl group. These are known

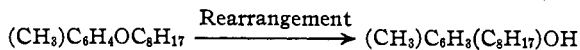
¹⁶ Wurtz, *Ann.*, **125**, 118 (1863).

¹⁷ Williamson, *J. Chem. Soc.*, **4**, 106 (1851).

¹⁸ Claisen, *Ann.*, **237**, 261 (1887); **401**, 21, 119 (1914); *Ber.*, **45**, 3157 (1912); **58**, 275 (1925); *Z. angew. Chem.*, **36**, 478 (1923).

¹⁹ Van Alphen, *Rec. trav. chim.*, **46**, 799 (1927); Heller, *Ber.*, **45**, 418 (1912); Bucherer and Grolée, *ibid.*, **39**, 986 (1906); Kursanov, *J. Russ. Phys.-Chem. Soc.*, **48**, 1172 (1914); Eijkman, *Chem. Zentr.*, **I**, 1597 (1904); **I**, 814 (1905).

to be stable and will not rearrange except under unusual conditions. It was therefore of interest to see whether these long-chain ethers would rearrange at higher temperatures. This would explain the substituted phenols obtained by König and Schrauth, by condensing unsaturated hydrocarbons at higher temperatures. *o*-Cresyl di-isobutyl ether was therefore gently refluxed for five hours in the presence of a mixture of zinc chloride and hydrochloric acid. A crystalline solid was obtained which was shown to be di-isobutyl *o*-cresol



The mechanism then proposed for all these condensations of unsaturated compounds with phenols would constitute an addition of hydrogen sulfate to the ethylenic linkage and a subsequent elimination of the acid with the formation of an ether. This ether in the case of saturated alkyl chains is stable and will not rearrange. In the case of more negative or heavier groups, rearrangement takes place with the formation of the corresponding substituted phenol.

Experimental Part

Condensation Method.—The method followed in these condensations is based upon work reported in earlier articles.²⁰

One molecular weight of the cresol or phenol was weighed into a 500-cc. Erlenmeyer flask. To this was added one mole of the unsaturated hydrocarbon, care being taken to avoid excessive evaporation. The flask was well corked and the contents shaken until complete solution had taken place. The mixture was surrounded by an ice and salt bath and allowed to come to zero degrees. Ninety-eight grams of sulfuric acid was weighed out and transferred to a buret. Two drops of sulfuric acid were carefully added. The cork was replaced and the flask thoroughly shaken, keeping the whole immersed in the freezing mixture. The remaining sulfuric acid was then added drop by drop with constant stirring and shaking. At no time was the temperature allowed to go over zero degrees. If this precaution is not observed side reactions are favored and a marked decrease in the yield is noticed. After half of the sulfuric acid has been added further addition does not increase the temperature greatly and the remainder can be added fairly rapidly.

The flask was then stoppered with a cork through whose bore was placed a calcium chloride drying tube to exclude moisture and to allow any gases formed to escape. The mixture, which was almost colorless and mobile at first, turned a pink, brown or red color on standing, dependent upon the phenol or cresol used, and assumed a heavy viscous appearance. The flask was allowed to remain in the bath until the ice had melted, and then after shaking was allowed to stand for one week at room temperature with occasional shaking. The viscosity seemed to increase slowly until it reached a constant value after four or five days.

The mixture was loosened from the walls of the vessel with ice water. Five molar, ice cold, sodium hydroxide was then added until the whole solution was just alkaline. On standing an oil separated at the top of the liquid. This was removed in a separatory funnel. In some cases it was more convenient to extract with ether and then evaporate the ether on a water-bath.

²⁰ Niederl, THIS JOURNAL, 50, 2230 (1928); 51, 2426 (1929).

The separate oil was washed twice with 50-cc. portions of dilute alkali (5%). It was then washed with two 50-cc. portions of saturated salt solution and then with 25 cc. of distilled water.

The liquid was dried over anhydrous potassium carbonate overnight, then transferred to an Erlenmeyer flask and a few bright pieces of sodium were introduced. After being left overnight effervescence ceased and the liquid was then distilled over a small piece of sodium. This precaution was necessary to remove the last traces of cresol or amyl alcohol, which may have been formed in the reaction as a by-product. The distillate thus obtained was then fractionated several times.

s-Amyl *m*-Cresyl Ether, 2-*m*-Cresoxyptane, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)\text{OC}_6\text{H}_4(\text{CH}_3)$.— This compound was obtained by applying the above method to amylene (b. p. 35–37°) and *m*-cresol. The fraction first collected was between 210–245°. Upon redistillation most of the liquid came over between 235–238°. The material was a clear mobile liquid which had a faint aromatic odor: b. p. 238° (uncorr.); n_D^{21} 1.500; sp. gr. 0.920 (20°).

Anal. Calcd. for $\text{C}_{12}\text{H}_{18}\text{O}$: C, 80.89; H, 10.11; mol. wt. 178. Found: C, 80.57; H, 10.77; mol. wt. 179.6.

The above ether was nitrated, using the following method: 20 cc. of concentrated sulfuric acid was mixed with 1 cc. of the condensation product. Concentrated nitric acid was added drop by drop until the vigorous reaction had ceased; 5 cc. was added in excess and the whole warmed on a water-bath until brown fumes ceased to be given off.

The reaction mixture was then poured into 200 cc. of water, when a yellowish-brown precipitate came out on standing. The precipitate was washed with water, a limited quantity of dilute sodium bicarbonate solution and then again with small portions of water. The brown mass was dried on a porous plate and recrystallized from 75% alcohol.

The material on recrystallization gave dark brown needles melting at 106°, which was shown to be trinitro-*m*-cresol. This product is probably formed on hydrolysis of the ether by the sulfuric acid and then nitration of the freed cresol.

Anal. Calcd. for $\text{C}_7\text{H}_5\text{N}_3\text{O}_7$: N, 17.29. Found: N, 17.01.

s-Amyl *m*-cresyl ether was also prepared by the following method:²¹ 14 g. of sodium was dissolved in 200 cc. of absolute ethyl alcohol in a three-necked flask fitted with a reflux condenser. While the last bit of sodium was dissolving, 65 g. of *m*-cresol was added through a dropping funnel. The whole was refluxed for twenty minutes. Through the same dropping funnel extending below the level of the liquid, amyl bromide prepared by the method of Wurtz¹⁶ was added drop by drop with constant refluxing. After all the halide had been added, refluxing was continued for two hours more. Sodium bromide separated out in less than twenty minutes and the flame had to be kept low to avoid excessive bumping. At the end of two hours the flask was allowed to cool and its content filtered with suction from the separated sodium bromide. The filtrate was put in a distilling flask and the alcohol distilled off.

The oil was separated from more sodium bromide, which had come out, by extraction with ether. The ether extract was washed with dilute sodium hydroxide solution, then with water and dried over calcium chloride. It was next treated with metallic sodium to remove any alcohol or cresol still left. The ether was evaporated and the oil fractionated. The major portion came over between 234–238°: b. p. 238° (uncorr.); n_D^{21} 1.496; sp. gr. 0.915 (20°).

Anal. Calcd. for $\text{C}_{12}\text{H}_{18}\text{O}$: C, 80.89; H, 10.11. Found: C, 80.82; H, 10.11.

On nitrating, as described before, trinitro-*m*-cresol was also obtained.

By applying the procedure given for amylene and *m*-cresol to phenol and the other cresols the following products were obtained.

²¹ Williamson, *J. Chem. Soc.*, 4, 106 (1851).

s-Amyl *p*-Cresyl Ether, 2-*p*-Cresoxyptane, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)\text{OC}_6\text{H}_4(\text{CH}_3)$.—The crude product distilled between 220–240°. This on careful redistillation gave a product which boiled fairly constantly between 223–225°; b. p. 225 (uncorr.); sp. gr. 0.920 (20°); n_D^{21} 1.505.

s-Amyl *o*-Cresyl Ether, 2-*o*-Cresoxyptane, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)\text{OC}_6\text{H}_4(\text{CH}_3)$.—The crude product distilled between 210–240°. On fractionation most of the material came over between 231–234°; b. p. 234°; n_D^{21} 1.493; sp. gr. 0.915 (20°).

The application of the condensation process to di-isobutylene, phenol and the cresols yielded the following products.

Di-isobutyl Phenyl Ether, 2,2,4-Trimethyl-4-phenoxyptane, $\text{CH}_3\text{C}(\text{CH}_3)_2\text{CH}_2\text{C}(\text{CH}_3)_2\text{OC}_6\text{H}_5$.—The material obtained was a clear, colorless liquid which solidified to needle-like crystals on prolonged cooling in an ice and salt bath. The material distilled with slight decomposition at atmospheric pressure. It distilled at 190° at 40 mm.; m. p. 12°; b. p. 258° (760 mm.); 190° (40 mm.); sp. gr. 0.950 (20°); n_D^{21} 1.510.

Anal. Calcd. for $\text{C}_{14}\text{H}_{20}\text{O}$: C, 81.55; H, 10.68. Found: C, 80.49; H, 10.47.

By applying the Williamson method to di-isobutyl bromide prepared by the method of Kondakow²² and sodium phenolate, an ether was obtained which showed the following physical constants: m. p. 11°; b. p. 193° (40 mm.); n_D^{21} 1.505; sp. gr. 0.930 (20°).

On nitration of di-isobutyl phenyl ether after the method described under amyli-*m*-cresyl ether, a product was obtained which melted at 120° and was shown to be picric acid by a mixed melting point. This product was obtained from both the condensation product and the synthesized ether.

p-Cresyl Di-isobutyl Ether, 2,2,4-Trimethyl-4-*p*-cresoxyptane, $\text{CH}_3\text{C}(\text{CH}_3)_2\text{CH}_2\text{C}(\text{CH}_3)_2\text{OC}_6\text{H}_4(\text{CH}_3)$.—A clear liquid was obtained which was purified by fractionation: b. p. 272° (uncorr.); n_D^{21} 1.470; sp. gr. 0.889 (20°).

Anal. Calcd. for $\text{C}_{15}\text{H}_{20}\text{O}$: C, 81.82; H, 10.91. Found: C, 81.65; H, 10.91.

m-Cresyl Di-isobutyl Ether, 2,2,4-Trimethyl-4-*m*-cresoxyptane, $\text{CH}_3\text{C}(\text{CH}_3)_2\text{CH}_2\text{C}(\text{CH}_3)_2\text{OC}_6\text{H}_4(\text{CH}_3)$.—The crude oil distilled from 250–275°. On fractionation the portion from 269–273° was collected; b. p. 273° (uncorr.); sp. gr. 0.895 (20°); n_D^{21} 1.476.

Anal. Calcd. for $\text{C}_{15}\text{H}_{20}\text{O}$: C, 81.82; H, 10.91. Found: C, 81.99; H, 11.12.

Di-isobutyl *o*-Cresyl Ether, 2,2,4-Trimethyl-4-*o*-cresoxyptane, $\text{CH}_3\text{C}(\text{CH}_3)_2\text{CH}_2\text{C}(\text{CH}_3)_2\text{OC}_6\text{H}_4(\text{CH}_3)$.—B. p. 271° (uncorr.); m. p. 6° (uncorr.); sp. gr. 0.881 (20°); n_D^{21} 1.472.

Di-isobutyl *o*-Cresol, $\text{CH}_3\text{C}(\text{CH}_3)_2\text{CH}_2\text{C}(\text{CH}_3)_2\text{C}_6\text{H}_3(\text{CH}_3)\text{OH}$.—Hydrogen chloride was bubbled through 20 g. of di-isobutyl *o*-cresyl ether at zero degrees until 0.5 g. increase in weight was observed; 1 g. of anhydrous zinc chloride was added and the whole heated in an oil-bath to 200° for five hours. The mixture was steam distilled. An oil separated out which solidified to needle-like crystals on cooling. The phenolic properties of the compound are illustrated by its reaction with aqueous sodium hydroxide solution (formation of a soap-like sodium salt, soluble in water with difficulty) and of its alcoholic solution with ferric chloride with the formation of a transient green color; m. p. 49–50° (uncorr.).

Anal. Calcd. for $\text{C}_{15}\text{H}_{20}\text{O}$: C, 81.82; H, 10.91. Found: C, 82.17; H, 10.37.

Summary

The condensation of unsaturated hydrocarbons with phenolic type compounds was carried out. Ethers were obtained. This work, therefore, affords a method of preparing certain alkyl phenyl ethers.

²² Kondakow, *J. prakt. Chem.*, [2] 54, 450 (1897).

A mechanism was proposed not only for this condensation reaction but also for all similar condensation reactions between compounds containing the ethylenic linkage and phenols in the presence of sulfuric acid.

Further work, as to the condensation possibilities of unsaturated hydrocarbons, mono- and di-olefins, alcohols, (esters, ethers), aldehydes (acetals) and ketones, acids, nitriles, amines and halides with mono- and polyhydroxy phenols is being carried out.

NEW YORK, N. Y.

[CONTRIBUTION FROM THE INSECTICIDE DIVISION, BUREAU OF CHEMISTRY AND SOILS]

NEONICOTINE AND ISOMERIC PYRIDYLPYPERIDINES¹

By C. R. SMITH

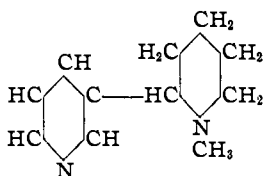
RECEIVED OCTOBER 27, 1930

PUBLISHED JANUARY 12, 1931

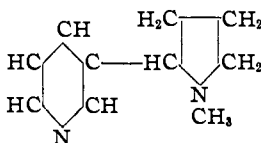
In a previous publication² on the interaction of sodium, pyridine and oxygen, the principal products isolated by the procedure outlined were γ,γ -, α,α -, β,γ - and β,β -dipyridyls. Later work has shown that, in addition to these compounds, there are formed water-insoluble bases boiling between 200 and 270°, richer in hydrogen than the dipyridyls, and a water-soluble base of especial interest which has been isolated and identified as β -pyridyl- α -piperidine. This compound has been called "neonicotine" because of its resemblance to nicotine in chemical structure and its toxicity to aphids and other soft-bodied insects.³

Neonicotine, $C_{10}H_{14}N_2$, resembles nicotine in structure more than does any of the other isomeric pyridylpiperidines. It is the only one of the pyridylpiperidines that has yet been prepared which shows any marked toxicity to insects.

A comparison of the formulas of neonicotine and nicotine reveals the similarity in structure. The N-methylneonicotine is shown in Formula I for comparison with nicotine (II)



Methylneonicotine I



Nicotine II

¹ Presented as a part of the Insecticide Symposium before the Division of Agricultural and Food Chemistry at the 79th Meeting of the American Chemical Society, Atlanta, Georgia, April 7 to 11, 1930.

² C. R. Smith, *THIS JOURNAL*, **46**, 414 (1924).

³ Toxicity results are to be reported elsewhere in a joint publication with Dr. C. H. Richardson and H. H. Shepard.