in 185 cc. of methanol was added 15 g. of concd. sulfuric acid and the solution was refluxed for two hours. Upon dilution with 200 cc. of water the ester separated; yield, 82% (43.5 g.). It was recrystallized from water, forming long rod-like crystals; m. p. 225–226°.

Anal. Calcd. for $C_9H_{10}O_8NAs$: As, 22.37. Found: As, 22.43, 22.45.

Reduction of this methyl ester with cold ferrous hydroxide yielded 3-hydroxy-1,4-benzisoxazine-6-arsonic acid; yield, 66%. It crystallized from water as white diamond-shaped crystals.

Anal. Calcd. for $C_8H_8O_5NAs$: As, 27.45. Found: As, 27.45, 27.50.

Summary

1. 4-Hydroxyphenylarsonic acid was condensed with ethylene and trimethylene chlorohydrins to form β-4-arsonophenoxyethanol and γ-4-arsonophenoxypropanol.

2. Nitration of β-4-arsonophenoxyethanol and γ-4-arsonophenoxypropanol was characterized by three types of reactions. Treatment with nitric acid (sp. gr. 1.50) resulted in the introduction of one or two nuclear nitro groups meta to the arsonic acid group, conversion of the alcohol group to its nitro ester, or oxidation of the alcohol group to the corresponding acid. Depending upon the conditions employed these reactions occurred either separately or simultaneously. Satisfactory methods for preparation and separation of the nitration products were devised.

3. β-2-Nitro-4-arsonophenoxyethyl nitrate and γ-2-nitro-4-arsonophenoxypropyl nitrate were hydrolyzed with 3 *N* hydrochloric acid to yield the corresponding mono-nitro compounds.

4. β-2-Amino-4-arsonophenoxyethanol, β-2,6-diamino-4-arsonophenoxyethanol and γ-2-amino-4-arsonophenoxypropanol were obtained by reduction of the corresponding nitro compounds. Some of the derivatives of the first compound were prepared.

5. Arseno-3,3′-dinitro-4,4′-di-β-phenoxyethyl nitrate, arseno-3,3′-dinitro-4,4′-di-β-phenoxyethanol and arseno-3,3′-diamino-4,4′-di-β-phenoxyethanol were prepared from the corresponding arsonic acids by reduction with hypophosphorous acid.

6. 3-Amino-4-β-hydroxyethoxyphenylarsenious oxide, 3-chloro-4-β-hydroxyethoxyphenylarsenious oxide, and 4-β-hydroxyethoxyphenylarsenious oxide were prepared from the corresponding arsonic acids by reduction with sulfurous acid, employing hydriodic acid as a catalyst. 3-Amino-4-β-hydroxyethoxyphenyldichloroarsine hydrochloride was prepared from the corresponding oxide.

LINCOLN, NEBRASKA RECEIVED JUNE 28, 1934

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE WASHINGTON SQUARE COLLEGE OF NEW YORK UNIVERSITY]

The Addition of Phenols to Arylenes. The Synthesis of Phenylthymol and its Isomers

BY JOSEPH B. NIEDERL AND CHARLES H. RILEY[1]

Theoretical Part

As the addition of phenols to unsaturated compounds of the acyclic series has been shown to be a general reaction[2] it was therefore considered highly desirable to extend these studies to the aromatic hydrocarbons. In the series of aromatic hydrocarbons with an unsaturated side-chain only styrene appears to have been subjected to such studies, yielding *x*-phenyl-α-(*p*-hydroxyphenyl)-ethane and α-phenyl-α-(*o*-hydroxyphenyl)-ethane, respectively.[3]

It was decided to study higher hydrocarbons with longer side chains and phenylpropylene ($C_6H_5—CH=CH—CH_3$) was chosen for this purpose with the expectation that interesting aryl derivatives of thymol would result. Phenylpropylene ($C_6H_5—CH=CH—CH_3$) prepared from phenylethylcarbinol by dehydration was therefore condensed with the cresols and a condensation product was obtained in each case. The condensing agent was a mixture of concentrated sulfuric acid and glacial acetic acid and the reac-

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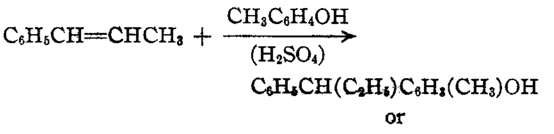
(1) From the thesis presented by Charles H. Riley to the Faculty of the Graduate School, of New York University, in partial fulfilment of the requirement for the degree of Master of Science, 1933.

(2) Niederl and co-workers, THIS JOURNAL, **50**, 2230 (1928); **51**, 2426 (1929); **53**, 272, 806, 1928, 3390 (1931); **54**, 1063 (1932); **55**, 284, 2571, 3025, 4151, 4549 (1933); **56**, 1966 (1934); *Monatsh.*, **51**, 1028 (1929); **60**, 150 (1932); *Z. angew. Chem.*, **44**, 467 (1931); **46**, 395 (1933).

(3) Koenigs, *Ber.*, **23**, 3144 (1890); Koenigs and Carl, *ibid.*, **24**, 3889 (1891); Koenigs and Mai, *ibid.*, **25**, 2650 (1892).

tion proceeded in a normal manner as described in the above-mentioned publications.

Obvious structural considerations reveal the possibility of the phenol adding on either to the alpha or the beta carbon atom, yielding in one case a substituted diphenylmethane compound, in the other a substituted diphenylethane product, respectively, as follows



$$C_6H_5CH{=}CHCH_3 + \xrightarrow[(H_2SO_4)]{CH_3C_6H_4OH} \begin{array}{c} C_6H_5CH(C_2H_5)C_6H_3(CH_3)OH \\ \text{or} \\ C_6H_5CH_2CH(CH_3)C_6H_3(CH_3)OH \end{array}$$

In an attempt to determine whether alpha or beta addition of the phenol occurred, a small amount of phenylpropylene in acetic acid was treated with hydrogen bromide gas, upon the assumption, verified in many cases, that hydrogen bromide would add to phenylpropylene in the same manner as sulfuric acid, the cationoid condensing agent used, or phenol. The brominated hydrocarbon formed was hydrolyzed to an alcohol by refluxing with dilute sodium hydroxide forming either methylbenzylcarbinol $C_6H_5CH_2CHOHCH_3$ or ethylphenylcarbinol $C_6H_5CHOHCH_2CH_3$ or both. Since the iodoform reaction is characteristic of compounds containing the —$CHOHCH_3$ group, iodoform should be obtained from methylbenzylcarbinol upon the addition of iodine to the carbinol in potassium hydroxide solution; ethylphenylcarbinol does not possess the —$CHOHCH_3$ grouping and therefore should not give the iodoform reaction.

The carbinol obtained by hydrolyzing the brominated hydrocarbon was treated with iodine in potassium hydroxide solution but no iodoform could be detected by odor, or separated in a pure state, due to the stronger odor and other physical properties of the carbinol. This solution, however, when warmed with aniline and potassium hydroxide gave a pronounced odor of carbylamine or phenyl isocyanide indicating that iodoform was present.

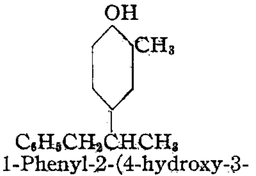
Phenylpropylene, ethylphenylcarbinol and methylbenzylcarbinol were treated in the same manner. The phenylpropylene and ethylphenylcarbinol gave no carbylamine reaction but the methylbenzylcarbinol gave a carbylamine reaction.

This would indicate that upon the addition of hydrobromic acid to phenylpropylene, α-phenyl-β-bromopropane is formed. Assuming the addition of the cresol to phenylpropylene is the same as the addition of the anionoid of hydrobromic acid, it would follow that the cresols added in a similar manner, namely, anionoidic to the beta carbon atom. This assumption would also be in harmony and in analogy with the fact that the addition of the cresols to related systems, *i. e.*, allyl and cinnamyl alcohol, propylene and allyl halides, has been shown to take place in an identical manner.[4]

Aside from the possibility of α- or β-addition as discussed above, it was also necessary to consider whether addition takes place ortho or para to the phenolic hydroxyl group. The many systems so far studied in this Laboratory[4] indicate that in case of *o*-cresol the addition takes place para to the hydroxyl group (I), whereas in the case of *p*-cresol the addendum must necessarily go in ortho position to the hydroxyl group (II). In the case of *m*-cresol, *o*- and *p*-addition is possible (III, IV) although it has been shown that *o*-addition appears to predominate (III) under the given reaction conditions.[4b,d,5]

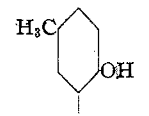
The structural formulas of the condensation products described herein then appear to be

I



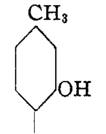
1-Phenyl-2-(4-hydroxy-3-methylphenyl)-propane

II



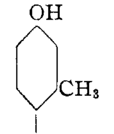
1-Phenyl-2-(2-hydroxy-5-methylphenyl)-propane

III



1-Phenyl-2-(2-hydroxy-4-methylphenyl)-propane "Phenyl thymol"

or



1-Phenyl-2-(4-hydroxy-2-methylphenyl)-propane "Phenyl-iso-thymol"

Experimental Part

Preparation of Phenylpropylene.—One mole of ethyl bromide was added drop by drop to one mole of magnesium ribbon cut up in small pieces in one liter of anhydrous

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[4] (a) Niederl, Smith and McGreal, This Journal, **53**, 3390 (1931); (b) Niederl and Storch, *ibid.*, **55**, 284, 4549 (1933); (c) Sowa, Hinton and Nieuwland, *ibid.*, **54**, 3694 (1932); (d) Smith and Niederl, *ibid.*, **55**, 4151 (1933).

[5] Fries and Klostermann, *Ber.*, **39**, 871 (1906); Jordan, German Patent 501,723 (1926); Zincke and Gäbel, *Ann.*, **388**, 299 (1912); Niederl, *Monatsh.*, **60**, 150 (1932).

PHYSICAL CONSTANTS AND ANALYSES OF THE COMPOUNDS

	Temp., °C. m. p. or b. p.	Sp. gr. 20°	n^{23}_{D}	Carbon, % Calcd. 84.95 Found	Hydrogen, % 7.96 Found	Nitrogen, % 4.05 Found
I	200 (18 mm.)	1.058	1.576	84.49	8.14	
Phenylurethan	178					3.63
II	215–220 (28 mm.)	1.062	1.578	84.26	8.22	
Phenylurethan	123					3.80
III	200–205 (22 mm.)	1.047	1.577	85.37	7.81	
Phenylurethan	125					4.20

ether which was contained in a three-necked flask with reflux condenser attached. After the reaction was complete one mole of benzaldehyde was added drop by drop. The resulting compound was decomposed with a dilute hydrochloric acid and the resulting ethylphenylcarbinol isolated and distilled 118–122° at 23 mm. The carbinol was converted to phenylpropylene by heating to 150° in a distilling flask with condenser attached and adding 1 to 2 drops of concentrated sulfuric acid. The stopper of the flask was replaced immediately whereupon by continuing the heating the phenylpropylene distilled over with the liberated water. The resulting product was washed with water, dried over calcium chloride and redistilled at 175–178° collecting the fraction.

Condensation Method.—One molecular weight of the cresol was weighed into a 500-cc. round-bottomed flask and one mole of phenylpropylene was added. To this was added glacial acetic acid containing 20% of concentrated sulfuric acid where the sulfuric acid was equimolecular to the cresol and phenylpropylene. After refluxing gently for four hours the mixture was allowed to cool and 10% sodium hydroxide was added until the solution was alkaline. An oil separated on standing which was washed with 10% sodium hydroxide to remove any unreacted cresol. The oil which was insoluble in dilute alkali was washed with dilute hydrochloric acid, then twice with salt solution and finally with a small amount of water.

The separation and washing are facilitated by first extracting the oil with ether and then evaporating the ether prior to fractional distillation.

The above compounds were tested for bactericidal activity against staphylococcus aureus.[6] The following results were obtained:

I: phenol coefficient: 59
II: phenol coefficient: 82
III: phenol coefficient: less than 10

Summary

1. The studies in the addition reaction of phenols to the ethenoid and ethinoid linkage have been extended to include aromatic hydrocarbons with an unsaturated side chain.

2. The system studied was phenylpropylene and the three cresols. The condensation in all cases was found to be positive.

3. Phenylthymol appears to have been produced in the case of the *m*-cresol–phenylpropylene condensation, but no definite stand can be taken as to the exact amount. In the other two cases isomers of phenylthymol were prepared. The physiological properties of these new compounds are under investigation as well as their hydrogenation products, the arylated menthols.

4. The studies in condensations are being extended to longer chain arylenes.

NEW YORK CITY RECEIVED JULY 2, 1934

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[6] The authors desire to thank Dr. Wm. A. Feirer of Sharpe and Dohme, Inc., Philadelphia, for determining the phenol coefficients of these compounds.