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Antiseptics. IV.[1] Alkyl Catechols

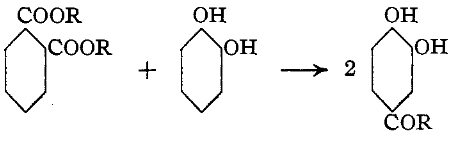
BY ELLIS MILLER, WALTER H. HARTUNG, HENRY J. ROCK AND FRANK S. CROSSLEY

Numerous investigations have shown that when an alkyl group is introduced into the nucleus of a phenolic compound the bactericidal activity increases with increase in the length of the alkyl chain. Thus, for example, in the series of 4-*n*-alkylresorcinols, the germicidal activity becomes greater as the alkyl group lengthens from ethyl, to propyl, to butyl and so on. A similar increase appears in the isoalkylresorcinol series,[1a] and in the homologous monoalkyl ethers of the dihydroxybenzenes[1b] as well as in the analogous thioethers.[1c]

A series of 4-alkylcatechols has now been prepared, in which a similar relationship is observed (*cf.* Table III).

The 4-alkylcatechols may be obtained from the corresponding acylcatechols by means of the Clemmensen reduction or by reducing with palladium catalyst. The intermediate ketone may be obtained by the Fries rearrangement of the appropriate ester of either catechol or guaiacol. In the latter case the reaction is accompanied by simultaneous demethylation.

The Fries isomerization of catechol esters was originally developed by Rosenmund and Lohfert.[2] These authors rearranged the dipropionate and dibutyrate of catechol into propionyl and butyryl catechols, respectively, using an additional equivalent of catechol and employing nitrobenzene as the solvent. They reported yields of ketone up to 70% of theoretical. By following their directions, it is possible to duplicate their results.[3] However, assuming that the reaction proceeds as follows



it develops that these investigators based their yields not on the formation of two molecules of ketone, but on one; hence, their yields actually were only 35%.

This reaction has now been modified and improved so that the nitrobenzene solvent may be replaced by the more volatile carbon bisulfide; the reaction product between the catechol and acid chloride need not be isolated. If the pure acid chloride is not available, it is possible to use the crude product obtained from the interaction of the acid and thionyl chloride without further purification. Or, again, the acid chloride, pure or crude, may be added to the mixture of catechol and aluminum chloride suspended in carbon bisulfide. Any of these modifications leads to uniformly good yields of ketone, usually 65–70%, frequently as high as 80%.

The rearrangement of guaiacol esters has been studied by Coulthard, Marshall and Pyman,[4] who prepared the corresponding acylguaiacols and observed that small amounts of the guaiacol ketones were demethylated to give the catechol ketones. By the use of proper amounts of reagents and proper working conditions, it is possible to bring about not only a migration of the acyl group of a guaiacol ester, but also a simultaneous demethylation, with the production of the catechol ketones in satisfactory yields, rather than the guaiacol ketones.

Experimental

Preparation of Guaiacol Esters.—In a flask equipped with a mechanical stirrer, dropping funnel and reflux condenser, the end of which was attached to a suitable absorption train for hydrogen chloride and sulfur dioxide, was placed a solution of equimolar parts of guaiacol and fatty acid. To the stirred solution was added 1.1 equivalents of thionyl chloride. Since the reaction is endothermic, the flask was heated gently during the addition of the thionyl chloride. Heating was continued until the evolution of hydrogen chloride and sulfur dioxide had practically ceased, whereupon the mixture was cooled, washed first with water and then with bicarbonate solution. After drying, the ester was distilled.

Conversion of the Esters of Guaiacol into Acylcatechols.—A typical experiment will be described. By substituting other esters in the place of guaiacol propionate, the other corresponding ketones may be obtained.

Into a 1-liter three-necked flask, fitted with reflux condenser, mechanical stirrer and dropping funnel, is placed 140 g. (1.05 moles) of anhydrous aluminum chloride and 300 ml. of carbon bisulfide. With constant stirring and over a period of fifteen minutes 90 g. (0.5 mole) of guaiacol

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(1) Previous papers of this series although not appearing under this title are (a) Dohme, Cox and Miller, THIS JOURNAL, **48**, 1688 (1926); (b) Read and Miller, *ibid.*, **54**, 1195 (1932); (c) Miller and Read, *ibid.*, **55**, 1224 (1933).

(2) Rosenmund and Lohfert, *Ber.* **61**, 2601 (1928).

(3) Hartung, Munch, Miller and Crossley, THIS JOURNAL, **53**, 4149 (1931).

(4) Coulthard Marshall and Pyman, *J. Chem. Soc.* 289 (1930).

propionate is added. With continued stirring the reaction flask is immersed in an oil-bath, the temperature of which is raised to 90° over a period of fifteen minutes and maintained there for an additional ten minutes. The dropping funnel is then replaced by a downward-distilling condenser and, with the oil-bath at 90°, the carbon bisulfide is removed over a period of about twenty-five minutes. Stirring is continued until the reaction mass becomes too viscous. The temperature of the oil-bath is now raised, during ten minutes, to about 140° and maintained there for an hour, after which heating is continued at 135–140° for another hour. The aluminum complex in the flask is decomposed by adding slowly through a dropping funnel 500 ml. of hydrochloric acid (1:1). As soon as the solid mass disintegrates, stirring is resumed and the mixture is refluxed until the solid is completely liquefied. The reaction mixture is now poured into a beaker and, when sufficiently cool, the supernatant oil is extracted with 175–200 ml. of benzene. The propionylcatechol may be recovered from the benzene solution by crystallization or by distillation. The amount of product varies between 43 and 47 g., or 51–55% of the theoretical.

It was found that optimum yields were obtained when the size of the charge did not exceed a half mole.

The data covering the ketones prepared by this method are included in Table I.

Ketones from Catechol.—As already mentioned, various adaptations of this procedure may be employed. Two typical examples will be given.

Example 1.—In a half-liter, three-necked flask, equipped with dropping funnel, mechanical stirrer and reflux condenser, the upper end of which is connected to a hydrogen chloride absorption apparatus, is placed 0.5 mole (55 g.) of catechol. The flask is heated in an oil-bath to 120° to melt the catechol and then, while stirring, there is added through the dropping funnel, over a period of about twenty minutes, one mole of acid chloride; stirring and heating are continued until the evolution of hydrogen chloride practically ceases (about thirty minutes). The product, substantially catechol diester, is allowed to cool and is used as indicated below.

In a 1-liter, three-necked flask, equipped with stirrer, dropping funnel and reflux condenser, is placed 2.5 moles (335 g.) of anhydrous aluminum chloride in 600 ml. of carbon bisulfide. To the agitated suspension is added a mixture of the diester, previously prepared, and an additional half mole (55 g.) of catechol;[5] the rate of addition is governed by the rate of refluxing, but usually it may be completed in twenty minutes. Stirring is continued at room temperature until the evolution of hydrogen chloride slows appreciably, after which the flask is warmed on an oil-bath to 80°. When the evolution of hydrogen chloride has practically ceased, the funnel is replaced by a downward-distilling condenser and the carbon bisulfide removed, while the temperature of the oil-bath is raised, over a period of an hour, from 80 to 135°. Stirring is discontinued when the reaction mass becomes too viscous. Heating is continued at 135–140° for about four and one-half hours. After cooling, the reaction mixture is decomposed by adding cautiously 500 ml. of dilute hydrochloric acid (1:1). When cool, the product may be removed and purified either by recrystallization or by distillation. A convenient method is to extract it with butyl alcohol, wash with water, dry and distil.

Example 2.—In a 100-ml. flask, connected to a hydrogen chloride absorption train, is placed 0.1 mole (11.9 g.) of thionyl chloride. The flask is heated in an oil-bath to 40° and 0.1 mole (11.6 g.) of caproic acid is dripped in over a period of ten minutes. The oil-bath temperature is raised to 70° and maintained at this level until no more hydrogen chloride and sulfur dioxide are given off (about one hour). The reaction mixture is stoppered and allowed to stand overnight.

In a half-liter flask, equipped with stirrer, dropping funnel and reflux condenser, connected to an absorption train, are placed 0.3 mole (39.9 g.) of anhydrous aluminum chloride and 0.1 mole (11 g.) of catechol in 100 cc. of carbon bisulfide. The mixture is stirred at room temperature for fifteen minutes and then at 40° (oil-bath temperature) for an hour. After this, the crude acid chloride, described above, is dripped in over a period of ten minutes. The temperature of the oil-bath is then raised to 70° over a ten-minute period and kept at 55–60° for an hour. During this time the carbon bisulfide evaporates and the temperature is raised to 140° and maintained at 135-140° for three and one-half hours.

The mixture is allowed to stand overnight and is decomposed by adding slowly 150 cc. of hydrochloric acid (1:1). On cooling, it is extracted with *n*-butanol, the extract is washed with water, and the caproylcatechol is recovered by distillation: yield, 14.5 g. of distillate, boiling at 220–225° (5 mm.) or 69.7%.

The data relating to the ketones obtained by the foregoing procedures are given in Table I.

3-Acylcatechols

The products obtained are predominantly the 4-acylcatechols. However, it is not unreasonable to expect at least small amounts of the 3-isomer. At first no attempt was made to isolate the 3-acylcatechols, but as the method of rearranging the catechol esters was improved and workable quantities of product became available, it was felt worth while to make a search for these compounds. Their presence was first suspected when, during the distillation of the ketones, a small fore-run with different physical properties was obtained. In some cases, it was possible to separate the isomers by fractional crystallization from benzene, the 4-isomer being less soluble. In other cases, it was difficult to be sure of the purity of the 3-isomer.

The data relating to the 3-acylcatechols, which were isolated, are given in Table II.

It is noteworthy that in common with many other orthohydroxyacylphenols the products described in Table II are not reduced by palladium

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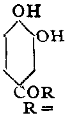
(5) It is best to dissolve the catechol in the diester just before using, as the catechol tends to crystallize out on standing. If crystallization occurs, the residue may be washed into the reaction flask with carbon bisulfide.

TABLE I

CATECHOL ALKYL KETONES

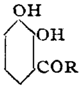


R =	Boiling range °C.	Mm.	M. p., °C.	% Yield through Catechol	% Yield through Guaiacol	Analyses, % Found C		Found H		Calcd. C	Calcd. H
n-Propyl			139		23–62	(Rosenmund and Lohfert)					
n-Butyl	210–220	4	93–94[a]	50		67.85[b]	68.51	5.77	6.40	68.00	7.27
Isobutyl	200–210	4	106.5–107.5	69		68.17[c]	68.06	7.28		68.00	7.27
n-Amyl	212–220	4	93.8	72	30–47[d]	(Coulthard, Marshall and Pyman)					
Isoamyl			73–73.5	60		68.75		7.73		69.20	7.75
n-Hexyl[e]			78–79		8–17						
n-Heptyl	225	5	95.5–96	50		71.08		8.57		71.14	8.54

[a] Coulthard, Marshall and Pyman give m. p. 143–144°. [b] These values are obtained if the ketone is recrystallized from benzene. If the product is precipitated from dioxane solution by the addition of water, better appearing crystals are obtained and the melting point rises to 100–101°. On analysis this material gave C, 65.35 and 65.09; H, 7.13 and 7.52; these values agree for either a half molecule of water or a half molecule of dioxane of crystallization. [c] The authors are indebted to Dr. Louise Kelley for these analyses. [d] A by-product, characterized by Coulthard, Marshall and Pyman[4] as 3-methoxy-4-hydroxycaprophenone, was obtained. [e] The amount of *n*-heptoylcatechol obtained was so small that all of it was needed in the preparation of heptylcatechol for bacteriological testing.

TABLE II

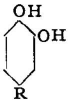
3-ACYLCATECHOLS



R =	Boiling range °C.	Mm.	M. p., °C.	Analyses, % Found C		Found H		Calcd. C	Calcd. H
Ethyl	182–187	5	102.5–103.5						
Isobutyl			93–95	68.06	68.17	7.28	7.14	68.0	7.27
Isoamyl	195–205			69.97		8.03		69.2	7.75
n-Heptyl	210–220	4	87–88	70.99		8.57		71.14	8.54

TABLE III

4-ALKYLCATECHOLS



R =	Boiling range °C.	Mm.	M. p., °C.	% yield (catalytic reduction)	Analyses, % Found C		Found H		Calcd. C	Calcd. H	Phenol coefficient (Staph. aur.)
n-Butyl	143–147	5		75							29
n-Amyl	158–159	7		86	72.81	72.77	8.95	8.99	73.28	8.95	
Isoamyl	155–160	6	55.5–58.5	70.5	72.98	73.12	8.79	8.80	73.28	8.95	
n-Hexyl	164–169	5		67–73	74.04	74.11	9.33	9.39	74.16	9.34	129
Isohexyl	161–164	5		84	73.39	73.49	9.32	9.41	74.16	9.34	
n-Heptyl[a]	195–200	12	40	71							177
n-Octyl	178	5	40	71	74.03	74.31	9.92	9.97	75.62	9.98	

[a] Analysis omitted for lack of material. See note (*e*) under Table I.

catalyst, thus confirming the belief that they contain an orthohydroxyl group.

Reduction of the Ketones

The catalytic method[6] is effective and convenient and it has been employed on a fairly large scale with unimpaired efficiency. The Clemmensen method gives less satisfactory yields. For example, 35 g. of caproylcatechol was stirred for ten hours in a boiling mixture of dilute hydrochloric acid and amalgamated zinc, 15 g. of product distilling at 175–178 (6 mm.) was obtained yield 46%.

The data relating to the 4-alkylcatechols is assembled in Table III.

Summary

1. Methods have been developed for the synthesis, in satisfactory yields, of 4-acylcatechols by the Fries isomerization of the esters of guaiacol, accompanied by simultaneous demethylation; or, better, by the rearrangement of the esters of catechol.

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[6] Hartung and Crossley, THIS JOURNAL, **56**, 158 (1934).

2. During the rearrangement of the catechol esters small amounts of 3-acylcatechols are formed.

3. The 4-acylcatechols may be converted into the corresponding alkylcatechols.

4. The alkylcatechols are effective germicides. The phenol coefficient increases with the length of the alkyl chain.

GLENOLDEN, PENNA. RECEIVED AUGUST 10, 1937

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF NEW YORK UNIVERSITY]

The Photolysis of Azomethane. III. The Effect of Nitric Oxide and the Nature of the Primary Step[1,2]

BY THOMAS W. DAVIS, FRANCIS P. JAHN AND MILTON BURTON[3]

Hitherto it has been tacitly assumed[4] that azomethane decomposes almost entirely to form free methyl radicals and molecular nitrogen in one primary act. Patat and Sachsse,[5a] among others, have considered the possibility of a primary step yielding $N{=}NCH_3$ and CH_3. The $N{=}NCH_3$ radical has been assumed to be very unstable;[4a,5,6] although Patat and Sachsse[5a] have indicated the implications of an assumed stability, Patat[5b] has been inclined in favor of the assumption of the initial split into free radicals. In general, however, there has been no evidence for a valid conclusion as to the relative probabilities of the paths

$$CH_3N{=}NCH_3 + h\nu \longrightarrow C_2H_6 + N_2 \qquad (1)$$

$$CH_3N{=}NCH_3 + h\nu \longrightarrow 2CH_3 + N_2 \qquad (2)$$

$$CH_3N{=}NCH_3 + h\nu \longrightarrow CH_3 + N{=}NCH_3 \qquad (3)$$

Inasmuch as azomethane has been used as a source of free methyl radicals in estimating chain lengths,[4c] it is evidently important to have information as to the primary step.

Burton, Davis and Taylor[6,7] have shown that methyl radicals formed in the photolysis of azomethane do not disappear exclusively by the reaction

$$2CH_3 + M \longrightarrow C_2H_6 + M \qquad (15)$$

but that some probably disappear by an association reaction of the type

$$CH_3 + A \longrightarrow CH_3A \qquad (6)$$

where A is used to symbolize a molecule of azomethane. The product is itself a free radical.[8] The results obtained were consistent with the hypothesis that part of the primary step might be represented by reaction 1 as well as by reaction 2. Unfortunately, the evidence on this point was not conclusive.

One of us[9] discovered in a study of the pyrolysis of azomethane that nitric oxide almost completely inhibits any pressure change in the early stages of the reaction. Although such an observation is not directly interpretable[10] the result suggested the possibility of making use of a similar method for a direct determination of the nature of the primary reaction in the photolysis.[11]

Staveley and Hinshelwood[12] have made use of the assumption that nitric oxide reacts very rapidly with free radicals in order to detect the participation of radicals in reaction chains. In the work described below we have made use of the same assumption in determining the nature of the primary step in the photolysis of azomethane. Although we have attempted to avoid the pitfalls involved in kinetic studies dependent on pressure changes by studying the products of the photolyses analytically, it must be emphasized that our conclusions are based upon the assumption that

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[1] Abstract from a thesis to be submitted by Francis P. Jahn to the Graduate School of New York University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[2] Presented before the Division of Physical and Inorganic Chemistry at the Rochester Meeting of the American Chemical Society, Sept. 6, 1937.

[3] Present address: Department of Chemistry, University of California, Berkeley, Calif.

[4] *Cf.* (a) F. O. Rice and K. K. Rice, "The Aliphatic Free Radicals," The Johns Hopkins Press, Baltimore, Md., 1935, p. 140; (b) O. K. Rice and Sickman, *J. Chem. Phys.*, **4**, 242 (1936); (c) Allen and Sickman, THIS JOURNAL, **56**, 2031 (1934).

[5] (a) Patat and Sachsse, *Z. physik. Chem.*, **B31**, 105 (1935); (b) Patat, *Naturwissenschaften*, **23**, 801 (1935); *Nachr. Ges. Wiss. Göttingen, Math.-physik. Klasse*, Fachgruppen II, [N. F.] **2**, 77 (1936).

[6] Burton, Davis and Taylor, THIS JOURNAL, **59**, 1038 (1937).

[7] Burton, Davis and Taylor, *ibid.*, **59**, 1989 (1937).

[8] The comparatively low probability of reaction 15 is well illustrated in the work on the alkyl halides (*cf.* Bonhoeffer and Harteck, "Grundlagen der Photochemie," Verlag von Theodor Steinkopff, Dresden, 1933, p. 172) and in the work on acetone [Spence and Wild, *J. Chem. Soc.*, 352 (1937)]. In the former case the yield of ethane is negligible; in the latter, analyses show that there is a high probability that methyl disappears by other reactions, particularly at low temperatures (~20°).

[9] Jahn, unpublished work.

[10] The work cited in references 6 and 7 indicates that failure to observe a pressure increase may be due to a multifold effect involving reactions such as 1, 2, 6, 16 and 18. *Cf.* Riblett and Rubin, THIS JOURNAL, **59**, 1537 (1937).

[11] *Cf.* (a) Linnett and Thompson, *Trans. Faraday Soc.*, **33**, 501 (1937); (b) Thompson and Linnett, *ibid.*, **33**, 874 (1937).

[12] Staveley and Hinshelwood, *Proc. Roy. Soc.* (London) **A154**, 335 (1936); *Nature*, **137**, 29 (1936); *J. Chem. Soc.*, 812 (1936).