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Homologs of Salol. The Salicylates of the Isomeric Amyl Phenols and Amyl Cresols

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Since Nencki[1] established the principle that the salicylates of phenolic compounds were hydrolyzed within the animal body, giving rise to an internal antiseptic action, it has seemed desirable to prepare salicylates, and other esters, of phenols whose germicidal activity is greater than phenol itself.

It was thought that one or more of the salicylates of the alkyl substituted phenols or cresols, whose values in antisepsis are known to exceed greatly that of phenol, might hydrolyze at a rate comparable with salol and furnish a compound whose internal antiseptic properties would be superior to those of salol.

A large number of salol-like esters have been prepared since Nencki's[1] original publications[2-4] but most of the attempts in this direction have been made with phenols whose germicidal values, while greater than that of phenol, are less than those of amyl phenols, amyl cresols, and cyclohexyl phenols selected for study in this series.

The isomeric *n*-amyl phenols and *n*-amyl cresols were prepared in the usual manner, by reducing the corresponding ketone, according to the procedure of Clemmensen.[5] The ketones were made by the Fries isomerization, following details given by Coulthard, Marshall and Pyman[6] and Sandulesco and Girard.[7] The isomeric 4-chloro- and 6-chloro-*o*-cyclohexylphenols were furnished by Dow Chemical Company, Midland, Michigan.

s-Amyl-*p*-cresol was obtained by condensing *n*-amyl alcohol with *p*-cresol in the presence of anhydrous zinc chloride.[8] A rearrangement occurs, according to Niederl and Natelson,[9] yielding, not *n*-amyl-*p*-cresol, but 3-(1-methylbutyl)-*p*-cresol. Details of this preparation are given below. The nomenclature, with reference to the substituted cresols, follows that of Coulthard, Marshall and Pyman.[6]

(1) M. H. v. Nencki, *Compt. rend.*, **108**, 254 (1889).
(2) Mannich and Merz, *Arch. Pharm.*, **265**, 104 (1927).
(3) Krauz and Remenec, *Collection Czech. Chem. Comm.*, **1**, 610 (1929).
(4) Harris and Christiansen, *J. Am. Pharm. Assoc.*, **24**, 553 (1935).
(5) Clemmensen, *Ber.*, **47**, 51–63 (1914).
(6) Coulthard, Marshall and Pyman, *J. Chem. Soc.*, 280 (1930).
(7) Sandulesco and Girard, *Bull. soc. chim.*, [4] **47**, 1300 (1930).
(8) Merrill C. Hart, U. S. Patent 2,082,625, June 1, 1937.
(9) Niederl and Natelson, THIS JOURNAL, **53**, 272–7 (1931).

The salicylates were prepared by condensing the amyl phenol or amyl cresol with salicylic acid in the presence of phosphorus oxychloride in the usual manner. The reaction period varied from eighteen to sixty-six hours (*cf.* table). With the exception of the salicylate of 4-chloro-*o*-cyclohexylphenol, which was separated from the 4-chloro-*o*-cyclohexylphenol on the basis of the insolubility of the ester in 1% sodium hydroxide, the esters were fractionated from the unreacted phenol by distillation under reduced pressure.

The salicylates of the amyl phenols and amyl cresols are faintly colored, somewhat viscous oils with characteristic odor, and astringent effect upon taste. Yields of the esters were usually 40–50%, but in the case of the salicylate of 3-*n*-amyl-*p*-cresol, the yield of the ester did not vary much from 6.5%.

Attempts to prepare the salicylate of 6-chloro-*o*-cyclohexylphenol yielded only salicylic anhydride (m. p. 211–214°), probably due to steric hindrance.

The rates of hydrolysis of these esters compare very favorably with that of salol; thus salol, under the conditions of the experiment, required twenty-seven hours for complete hydrolysis; the time required for the other esters varied only a few hours from this (twenty-eight to thirty-four hours).

Experimental

3-(1-Methylbutyl)-*p*-cresol.—Five hundred and thirty-five g. (3.92 moles) of anhydrous zinc chloride was mixed with 508 g. (4.70 moles) of *p*-cresol (Eastman, m. p. 36°). The reaction mixture was heated to above 140° and 275 g. (3.12 moles) of *n*-amyl alcohol (Mallinckrodt, b. p. 134–138°) was added dropwise in the course of two hours and fifteen minutes. The temperature of the reaction mixture was maintained above the boiling point of the *n*-amyl alcohol, and refluxing was continued for three hours after its addition.

A crude fraction of the *s*-amylcresol, I, was obtained, yellowish in color, 292 g. (52.6%) (boiling 123–136° at 13 mm.). This was purified by shaking with a nine-fold excess of 1:1 sodium hydroxide, forming the sodium *s*-amyl-*p*-cresoxide, a viscous jelly insoluble in 1:1 sodium hydroxide. The viscosity of this material was reduced with 150 cc. of absolute methyl alcohol, and the resulting solution was shaken out with petroleum ether (b. p. 30–60°). The extracted sodium *s*-amyl-*p*-cresoxide was acidulated with hydrochloric acid, and the resulting oil was washed.

TABLE I

Name of ester (salicylate of)	Reaction period, hrs.	B. p. °C.	Pressures Mm.	Analyses (micro.), % Calcd. C	Calcd. H	Found C	Found H	Molecular weight[a] Calcd.	Found
o-*n*-Amylphenol	43.0	155–157	$B_{0.030}$	76.03	7.09	76.14	7.32	284.4	288.7
p-*n*-Amylphenol	18.0	178–180	B_{2}	76.03	7.09	75.86	7.49	284.4	284.4
3-*n*-Amyl-*o*-cresyl	21.0	141–145	$B_{0.004}$	76.48	7.43	76.41	7.35	298.4	302.4
5-*n*-Amyl-*o*-cresol	25.0	140–142	$B_{0.060}$	76.48	7.43	76.51	7.39	298.4	297.6
4-*n*-Amyl-*m*-cresol	22.5	156–160	$B_{0.008}$	76.48	7.43	76.25	7.54	298.4	300.2
3-*n*-Amyl-*p*-cresol	27.0	150–156	$B_{0.050}$	76.48	7.43	76.43	7.16	298.4	304.9
3-(1-Methylbutyl)-*p*-cresol	66.0	166–168	$B_{0.018}$	76.48	7.43	76.22	7.17	298.4	302.0
4-Chloro-*o*-cyclohexylphenol	27.0	M. p. 99.5–100°[b]		68.98	5.79	69.12	6.09	330.8	326.6

[a] Determined by hydrolysis with 0.5 *N* alcoholic potassium hydroxide.

[b] Faintly colored glistening plates from 95% ethyl alcohol.

dried and distilled. The distillate, II, consisting of 197 g. of water-white material (b. p. 124–130° at 13 mm.) was fractionated and yielded 140 g. (25.2%) of water-white distillate, III (b. p. 127–130° at 13 mm.). Most of III came over at 127–128°.

The petroleum ether extract gave up mostly high boiling (130–136° at 13 mm.) material.

The phenol coefficient of III, the *s*-amyl-*p*-cresol, as determined by the F. D. A. method at 37° using *aureus* "Reddish," was 100. The analyses of a fraction of III (b. p. 127–128° at 13 mm.) are given.

Anal. (Micro.) Calcd.: C, 80.85; H, 10.18. Found: C, 80.41; H, 10.22.

3,5-Dinitrobenzoate of *s*-Amyl-*p*-cresol.—This ester was prepared in the usual manner in pyridine. The compound was recrystallized from 95% ethyl alcohol, yielding minute yellow needles, m. p. 105°.

Anal. (Micro.) Calcd.: C, 61.28; H, 5.41; N, 7.52. Found: C, 61.28; H, 5.32; N, 7.70.

Preparation of Salicylates (General Procedure)

Salicylate of 3-*n*-Amyl-*o*-cresol.—To 31.5 g. (0.228 mole) of vacuum dried salicylic acid (m. p. 157–159°) in 200 cc. of boiling dry toluene were added dropwise with mechanical agitation 42.8 g. (0.24 mole) of 3-*n*-amyl-*o*-cresol (b. p. 140–143° at 17 mm.) in 60 cc. of dry toluene and 18.4 g. (0.12 mole) of phosphorus oxychloride (Eastman) in 100 cc. of dry toluene. Addition of these reagents required about an hour. Refluxing and mechanical stirring were continued for twenty-six hours longer (*cf.* table) until evolution of hydrogen chloride had ceased. The cold reaction mixture was washed with an excess of cold aqueous sodium bicarbonate until free from salicylic acid. The toluene layer was then washed with distilled water and dried over anhydrous magnesium sulfate. After removing the toluene under reduced pressure, the resulting oil was fractionated. The forerun consisting of 16.0 g. came over at 63–141° at 0.003 mm., 34.2 g. of the ester (47.8%) distilled over, b. p. 141–145° at 0.004 mm. This ester was a very faintly colored rather viscous oil.

Rate of Hydrolysis of Esters.—The speed of hydrolysis or saponification of the esters was determined by a method similar to that used by Bischoff and Hedenström[10] and Volwiler and Vliet.[11] In each determination approximately 3.3 milliequivalents of the ester was dissolved in 50.0 cc. of acetone, and 50.0 cc. of 0.469 *N* potassium hydroxide solution in aldehyde-free 95% ethyl alcohol was added, the temperature being maintained at 37° in an incubator. At definite intervals 5-cc. portions were pipetted from the mixture and placed immediately into 100 cc. of 0.01257 *N* hydrochloric acid. The excess of acid was then back-titrated with 0.00450 *N* aqueous potassium hydroxide, no distilled water being used in the operation and carbon dioxide being excluded as completely as possible.

Acknowledgment is made to Dr. John F. Norton and Mr. E. A. Gibson of the Bacteriological Laboratory of the Upjohn Company for the phenol coefficient determination, and to Mr. C. H. Emerson for the micro-analyses given.

Summary

1. The 3-(1-methylbutyl)-*p*-cresol has been prepared and its properties are given.

2. New homologs of salol, the salicylates of the amyl phenols and the amyl cresols, have been described.

3. The rates of saponification of these salol-like esters have been found to compare favorably with that of salol.

KALAMAZOO, MICH. RECEIVED DECEMBER 8, 1937

(10) Bischoff and Hedenström, *Ber.*, **35**, 3433 (1902).

(11) Volwiler and Vliet, THIS JOURNAL, **43**, 1672 (1921).