The one tertiary isomer is more soluble than any of the three secondary isomers which in turn are more soluble than any of the four primary isomers. The solubility increases as the hydroxyl group approaches the center of the molecule. Limitation of the comparisons to either the primary or the secondary group reveals that the more compact the molecular structure, the greater is the aqueous solubility. The solubility of all eight isomers decreases as the temperature increases from 20 to 30°.

GREENSBORO, N. C. RECEIVED APRIL 5, 1937

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE WASHINGTON SQUARE COLLEGE OF NEW YORK UNIVERSITY AND ST. JOHN'S UNIVERSITY]

Equimolar Condensations of Aldehydes with Phenols. The Preparation of Primary Saturated Alkylphenols[1]

BY JOSEPH B. NIEDERL, VICTOR NIEDERL, S. SHAPIRO[2] AND MARTIN E. MCGREAL

Condensation of carbonyl compounds (aldehydes and ketones) with multimolar quantities of a phenol usually results in the formation of the corresponding alkylidene-di-phenol.[3] Dianin and von Braun,[4] however, made the observation that saturated secondary or tertiary alkylphenols are obtained when the intermediate polymeric condensation products resulting from the action of hydrochloric acid upon a mixture consisting of several moles of a phenol and one mole of a ketone, aliphatic (di-*n*-propyl, methyl hexyl ketone and dichloroacetone) as well as aromatic ketones (acetophenone, ω-chloroacetophenone) are subjected to pyrolysis. The formation of saturated alkylphenols from ketone-phenol polymers was a rather unexpected observation and the expression "disproportionation" process was suggested by von Braun for this phenomenon.

In all of the above investigations multimolar quantities of phenol were used. It was the purpose of the research set forth in this communication to investigate equimolar condensations of saturated aliphatic aldehydes with phenols to establish experimentally the following: (a) whether it is possible to obtain mole for mole addition; (b) whether these additions take place analogous to the addition of halogen acids or hydrocyanic acid to the carbonyl bond, or whether the addition takes place as in aldol condensations; (c) to investigate the chemical nature of the intermediate polymer; and (d) to investigate the behavior of these aldehyde–phenol polymers upon pyrolysis, particularly as to the possibility whether a similar "disproportionation" could be observed in the aldehyde series as has already been established in isolated cases in the ketone and indane series.[5] Although the end-products, the saturated primary alkylphenols, could be identified easily, analysis of the intermediate polymeric condensation products did not lead to uniformly interpretable results. Some of these products, when reprecipitated, powdered and completely dried in a vacuum desiccator over phosphorus pentoxide for several months, gave results upon quantitative analysis which corresponded closely to polymeric alkylenephenols. The pyrolysis of the condensation products of phenols and the three cresols with the following aldehydes were studied.

Formaldehyde and phenol yielded a small amount of a cresol. Acetaldehyde and phenol (I) and the three cresols (II, III, IV) gave the corresponding ethylphenol and ethylcresols upon pyrolysis of the Claisen solution soluble polymeric condensation products. Substitution of vinyl acetate for acetaldehyde yielded similar polymers. Propionaldehyde (V), *n*- and isobutyraldehyde (VI, VII), *n*-valeric aldehyde (VIII) and *n*-heptaldehyde (IX) and phenol gave the respective alkylphenols. These primary saturated alkylphenols were purified by repeated fractional distillation, then analyzed and further characterized as crys-

(1) Presented before the Division of Organic Chemistry at the Pittsburgh meeting of the American Chemical Society, September, 1936.

(2) Several parts are taken from the thesis of S. Shapiro, presented to the Graduate School of New York University in partial fulfilment of the requirements for the degree of Master of Science.

(3) Schmidlin and Lang, *Ber.*, **43**, 2806 (1910); Claus and Trainer, *ibid.*, **19**, 3009 (1886); Moehlau and Koch, *ibid.*, **11**, 283 (1878); L. Claisen, *Ann.*, **237**, 261 (1887); Th. Zincke, *ibid.*, **363**, 255 (1908); E. K. Bolton, U. S. Patent 2,069,573 (1937); H. S. Rothrock, *ibid.*, 2,069,560 (1937).

(4) Dianin, *J. Russ. Phys.-Chem. Soc.*, **23**, 540 (1891); *Ber.*, **25**, 336 (1892); J. v. Braun, *Ann.*, **507**, 15 (1933).

(5) Niederl, Niederl and Reznek, THIS JOURNAL, **58**, 657 (1936); Weissberger, *Ber.*, **44**, 1438 (1911); Weger and Billmann, *ibid.*, **36**, 644 (1903); Kramer and Spilker, *ibid.*, **29**, 561 (1896); **33**, 2260 (1900); **23**, 3278 (1890); Moschner, *ibid.*, **33**, 737 (1900); Stoermer and Boes, *ibid.*, **33**, 3016 (1900).

TABLE I

No.	Phenol; HAc deriv.	Formulas	B. p., °C. 760 mm.	M. p., °C.	$n^{25}D$	Sp. gr.^{25}	Phenol coeff.	Analyses, % Calcd. C	Calcd. H	Calcd. N. E.	Found C	Found H	Found N. E.
I	*p*-Ethyl-	$C_8H_{10}O$	210–212		1.5239	1.0123	10	78.69	8.19		78.51	8.04	
	HAc deriv.	$C_{10}H_{12}O_3$		90				66.67	6.67		66.60	6.28	180
II	2-Methyl-4-ethyl-	$C_9H_{12}O$	223–228		1.5372	0.9944	11	79.41	8.82		79.75	8.62	
	HAc	$C_{11}H_{14}O_3$		125				68.04	7.26	194	68.23	7.05	195
III	3-Methyl-4-ethyl-	$C_9H_{12}O$	230–235		1.5362	.9956	10	79.41	8.82		79.52	8.70	
	HAc	$C_{11}H_{14}O_3$		131				68.04	7.26	194	68.15	7.09	193
IV	4-Methyl-2-ethyl-	$C_9H_{12}O$	215–221		1.5340	.9949	10	79.41	8.82		79.63	8.98	
	HAc	$C_{11}H_{14}O_3$		133				68.04	7.26	194	68.05	7.10	195
V	*p*-*n*-Propyl-	$C_9H_{12}O$	228–230		1.5379	.999	14	79.41	8.82		79.16	8.47	
	HAc deriv.	$C_{11}H_{14}O_3$		86				68.04	7.26	194	67.91	7.45	196
VI	*p*-*n*-Butyl-	$C_{10}H_{14}O$	238–242		1.4981	.9664	21	80.00	9.33		79.67	9.12	
	HAc deriv.	$C_{12}H_{16}O_3$		81				69.23	7.69	208	69.07	7.69	207
VII	*p*-Isobutyl-	$C_{10}H_{14}O$	235–239		1.5319	.9796	18	80.00	9.33		80.24	9.61	
	HAc deriv.	$C_{12}H_{16}O_3$		124–125				69.23	7.69	208	69.02	7.42	205
VIII	*p*-*n*-Amyl-	$C_{11}H_{16}O$	248–253		1.5272	.9621	20	80.36	9.76		80.69	9.35	
	HAc deriv.	$C_{13}H_{18}O_3$		90				69.95	8.52	222	70.16	8.25	225
IX	*p*-*n*-Heptyl-	$C_{13}H_{20}O$	271–278		1.5090	.9583	21	80.83	10.88		80.51	10.46	
	HAc deriv.	$C_{15}H_{22}O_3$		94				72.00	8.80	250	71.92	8.79	251

talline aryloxy-acetic acids, prepared according to Shriner and Fuson.[6]

Experimental

***p*-Ethylphenol, *p*-Ethyl-*o*-cresol, *p*-Ethyl-*m*-cresol, *o*-Ethyl-*p*-cresol.**—Molar mixtures of phenol or cresol and acetaldehyde were placed in a 2-liter 3-necked round-bottomed flask provided with a reflux condenser, a thermometer and a gas inlet tube extending to the bottom of the vessel. Two hundred cc. of glacial acetic acid was added and the reaction mixture cooled to about −5° by immersing the flask in an ice–salt mixture. A vigorous stream of dry hydrochloric acid gas was passed through the system for two hours and then the condensation product, a dark red oil, was poured into a large volume of cold water. A yellowish white precipitate formed which was washed repeatedly with cold and hot water, then filtered and dried; yield, almost quantitative. The thoroughly dry product was powdered, placed in a 250-cc. distilling flask and distilled under atmospheric pressure. The distillate, consisting of water, the respective phenol or cresol and the alkylated ethylphenol or ethyl cresol was taken up in ethyl acetate, this solution dried over calcium chloride and filtered. The solvent was distilled off and the residue fractionally distilled under atmospheric pressure. The lower boiling portion (about 30%) consisted mostly of the original phenol or cresol; the higher boiling portion (about 40%) was redistilled and consisted of the respective ethylphenol or ethylcresol. A charred residue (about 20%) remained in the distilling flask after pyrolysis.

Aryloxyacetic Acid (HAc Deriv.).—By the method of Shriner and Fuson, 1 g. of *p*-ethylphenol was dissolved in 5 cc. of a 33% sodium hydroxide solution and 1.5 g. of chloroacetic acid added. The mixture was shaken thoroughly and heated on a water-bath at 100° for one hour. The solution was then diluted with 15 cc. of water, acidified with dilute hydrochloric acid to congo red and extracted with 50 cc. of ether. The ether was washed with an equal volume of water and then shaken out with 25 cc. of a 5% sodium carbonate solution. This solution was acidified with dilute hydrochloric acid and the *p*-ethylphenoxyacetic acid which precipitated out filtered and dried on porous tile. It was recrystallized from diisobutylene. The cresoxyacetic acids were prepared in the same manner.

***p*-*n*-Propylphenol, *p*-*n*-Butylphenol, *p*-Isobutylphenol, *p*-*n*-Amylphenol, *p*-*n*-Heptylphenol.**—These compounds were prepared in a similar manner as described above, except that the reaction was carried out at room temperature and condensation was complete in two and one-half to three hours. The temperature inside the reaction vessel rose to 60 to 80° and diminishing temperature indicated completion of the reaction. The condensation product was then poured into cold water and a heavy oil separated out which was taken up in ethyl acetate. This solution was washed exhaustively with water, then dried and distilled under atmospheric pressure. The distillate, consisting of water, phenol and the corresponding alkylated phenol, was again taken up in ethyl acetate, dried and fractionally distilled under reduced pressure. The higher boiling fraction, representing the respective alkylated phenol, was purified by redistillation. The yield ranged from 20 to 40%.

The acetic acid derivatives were prepared as described above, except that wherever the final precipitate was an oil it was extracted from the aqueous solution with ether, the ether permitted to evaporate at room temperature, whereupon the acetic acid derivative crystallized. All the derivatives were recrystallized from diisobutylene.

The phenol coefficients given are the average of six tests, performed in 30% alcoholic solution with *staphylococcus aureus* at 37°. The authors are indebted to Dr. Wm. A. Feirer of the Mulford Biological Laboratories, Glenolden, Pa., for performing these tests. The authors are further indebted to the Lambert Pharmacal Co., St. Louis,

(6) Shriner and Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, 1935, p. 148.

Mo., for a research grant for the completion of this investigation.

Summary

Equimolar condensations of monohydroxyphenols with saturated aliphatic aldehydes were studied. It was found that polymers result in quantitative yields. Upon slow pyrolysis, these polymers yield the corresponding saturated primary alkylphenols. These types of condensations are being extended to unsaturated and aromatic aldehydes, reducing saccharides as well as to ketones, particularly cyclic ketones (cyclopentanone, cyclohexanone, alkyl cyclohexanones and camphor).

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Some Derivatives of Ortho-Hydroxyphenylmercuric Chloride

BY HANS P. ANDERSEN AND MERRILL C. HART

In earlier reports it has been shown that variations in structure have a limited influence on bacteriostatic properties of organic mercury compounds,[1] and that more complex structures were not as effective as mercury derivatives of hydrocarbons or phenols with limited substituents.[2] One very effective mercurial was found to be *o*-hydroxyphenylmercuric chloride, this compound also being bactericidal at some dilutions.[2] It seemed that possible derivatives of this compound could be prepared which would have similar properties.

Some imide derivatives of phenylmercuric nitrate have been described as being used in germicidal detergent or cosmetic compositions.[3]

In the present work some imide derivatives of *o*-hydroxyphenylmercuric chloride have been prepared and their bacteriological properties evaluated.[4] One has been found to be equally as good as the parent compound. It was found that, in general, imide derivatives were readily formed in alkaline solution, especially if the imide contained a carbonyl group. An attempt was made to prepare derivatives of pyrrole, auramine, carbazole and piperidine but only in the case of piperidine was a product obtained in the form of the hydrochloride. This was formed in the absence of alkali.

Although the simplest structures are most effective, it was thought that fatty acid derivatives might facilitate the *in vivo* activity by increasing diffusion into the surfaces in contact with the antiseptic. A few representative phenolmercuric fatty acid compounds have been prepared and described.

The table gives the results obtained together with melting points and analytical data.

TABLE I

Compound with $HOC_6H_4HgCl(o-)$	Yield, %	M. p., °C.	Mercury analyses, % Calcd.	Found	Inhibiting dilution to *Staph. aureus* in 5 min.
Succinimide	72.3	232–235	51.1	50.8	1-75,000[a,b]
Saccharine	53.7	242–243	42.5	42.1	1-10,000
Phthalimide	96.3	223–224	45.5	45.6	1-20,000
Piperidine	79.3	126	48.3[c]	47.8	1-30,000
Theobromine	51	145–165	40.8[d]	40.3	1-10,000
Barbituric acid	48	...	56.1	56.3	1-20,000
Acetic acid	...	150–151	56.8	56.7	1-40,000
Pelargonic acid	60.7	135	44.4	44.1	1-20,000
Oleic acid	64.3	95–96	34.8	34.98	1-20,000
Lauric acid	74	135.5–136.5	40.6	40.3	1-20,000
Myristic acid	72	135–136[e]	38.5	38.3	1-10,000
Palmitic acid	90	129–131	36.5	36.3	1-10,000
Stearic acid	70	135–137[e]	34.7	34.4	1-10,000

[a] This compound was bactericidal 1-1000. [b] Phenol control 1-80. [c] This is the mercury content of the hydrochloride. Calcd. for $C_{11}H_{15}OHgHCl$: Cl, 8.81. Found: Cl, 8.41. [d] Monohydrate. [e] Mixed melting points with pelargonic and lauric acid derivatives were depressed.

Experimental

***o*-Hydroxyphenylmercuric Succinimide.**—Three and three-tenths grams of succinimide in 18.7 cc. of water, was added to 10.95 g. of *o*-hydroxyphenylmercuric chloride in 25 cc. of warm alcohol. This was cooled as much as possible without forming a precipitate and then 18.7 cc. of 10% potassium hydroxide was added. After shaking and further cooling, 11 g. of crude product was obtained melting at 222°. This was recrystallized from 200 cc. of alcohol and 100 cc. of water to give a final yield of 72.3%. The melting point was 232–235°.

The other imide derivatives were made in the same manner using either water or alcohol, depending on which was the better solvent for carrying out the reaction.

***o*-Hydroxyphenylmercuric Piperidine Hydrochloride.**—Five cubic centimeters of piperidine was added to 16.4 g.

(1) Hart and Andersen, THIS JOURNAL, **56**, 2752 (1934).

(2) Hart and Andersen, *ibid.*, **57**, 1059 (1935). See also Phatak and Leake, *J. Pharmacol.*, **56**, 265 (1936).

(3) British Patent 432,689, July 31, 1935.

(4) We are indebted to Mr. E. A. Gibson, Bacteriological Laboratory, for these results.