due on fractionation with a 6-inch Widmer column gave the ketone. In hydrolyses with hydriodic acid, the cooled mixture was extracted with benzene. The benzene solution was washed with water, decolorized with sodium thiosulfate, washed with water and sodium bicarbonate solution and dried. The solvent was distilled and the residue on fractionation gave the ketone.

The results of the experiments are summarized in Table I.[6] The yields of the ketones from the β-keto esters varies from 69 to 81%. The yields of the β-keto esters from disubstituted acetic acid esters and acid chlorides vary from 51 to 74%.[3] The over-all yields of the ketones from the esters and acid chlorides vary from 38–58%. The synthesis therefore offers a satisfactory preparation of the ketones. The method may be extended to the preparation of phenyl ketones with substituents in the ring.

(6) Boiling points and melting points are corrected. Microanalyses are by Saul Gottlieb, Columbia University, New York, N. Y.

Summary

A convenient general method is described for the preparation of ketones of the type $RCOCHR_2$. Esters of the type $HCR_2CO_2C_2H_5$, in the form of their sodium enolates, are condensed with acid chlorides[3] to give β-keto esters of the type $RCOCR_2CO_2C_2H_5$, which on hydrolysis give the ketones.

The method represents an extension of the acetoacetic ester type of ketone synthesis.

DURHAM, N. C. RECEIVED JULY 7, 1941

[JOINT CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, PEIPING UNION MEDICAL COLLEGE, AND THE DEPARTMENT OF CHEMISTRY, FU JEN UNIVERSITY, PEKING, CHINA]

The Preparation and Properties of Three Isomeric *n*-Hexyl Cresols and their Chlorinated Derivatives

BY PETER P. T. SAH AND HAMILTON H. ANDERSON

6-*n*-Hexyl-*m*-cresol (1-hydroxy-3-methyl-6-*n*-hexylbenzene) was reported by Lamson and Brown[1] to be an active ascaricide. Although its anthelmintic activity is less than that of *n*-hexylresorcinol, it possesses the advantage of being less irritating to the mucous membranes of the gastro-enteric tract. Its mono-chloro derivative, 4-chloro-6-*n*-hexyl-*m*-cresol (1-hydroxy-3-methyl-4-chloro-6-*n*-hexylbenzene) was recently reported by Hartman and Schelling[2] to be an effective bactericidal substance, especially against staphylocci, streptococci, pyocyaneus, and the gram-negative bacilli when solutions are acidified to *p*H of 3 with the addition of hydrochloric or other acids. The toxicity, both local and systemic, was said to be comparatively low. The anthelmintic property of this compound had not been studied.

In view of these reports, we deemed it worthwhile to prepare from the isomeric cresols the isomeric *n*-hexylcresols and their monochloro derivatives so that a study of their biologic properties might be made. The effect of orientation and of chlorination of *n*-hexylcresols on the toxicity as well as other biologic activities will be published elsewhere.

The starting material of this synthesis was Chinese castor oil.[3] This was pyrolyzed with sodium hydroxide in a copper flask; the soap was thus decomposed to secondary octyl alcohol (methyl-*n*-hexylcarbinol). The crude secondary alcohol formed was then oxidized with potassium dichromate and sulfuric acid, first to methyl *n*-hexyl ketone[3] and then to *n*-caproic acid.[4] The acid, after purification by fractional distillation, was treated with thionyl chloride to form *n*-caproyl chloride.[5]

To convert the three isomeric cresols to the *n*-hexylchlorocresols, two methods were used. For the first method, the cresols were esterified with *n*-caproyl chloride to tolyl caproates. These esters, when subjected to Fries rearrangement,[6] were converted to the corresponding phenolic ketones (*n*-hexoyl-cresols) which were then reduced by Clemmensen's method[7] to the corresponding

(1) Lamson and Brown, *J. Pharm. Expil. Therap.*, **53**, 227 (1935).

(2) Hartman and Schelling, *Am. J. Surgery*, **46**, 460 (1939).

(3) (a) Kao and Ma, *Science Reports*, National Tsing Hua University, *A1*, 129 (1932). (b) Kao and Yen, *J. Chinese Chem. Soc.*, **2**, 21 (1934).

(4) Tseng, "Laboratory Manual of Organic Chemistry," National Peking University Press, 1935, p. 79.

(5) (a) Meyer, *Monatsh.*, **22**, 48 (1901); (b) Beilstein, "Handbuch d. org. Chem.," Bd. II, 1920, p. 324.

(6) (a) Blatt, *Chem. Rev.*, **27**, 413 (1940); (b) Baltzly and Bass, THIS JOURNAL, **55**, 4292–4294 (1933).

(7) (a) Gattermann and Wieland, "Die Praxis des organischen Chemikers," 1933, p. 372. (b) Read and Wood, "Organic Syntheses," Vol. XX, 1940, pp. 57–59. (c) Clemmensen, *Ber.*, **46**, 1840 (1913).

n-hexylcresols. By the reaction with a calculated amount of sulfuryl chloride,[8] the corresponding monochloro derivatives of the *n*-hexylcresols were obtained.

For the second method, the cresols were first chlorinated with a calculated amount of sulfuryl chloride to make the corresponding monochlorocresols. These were esterified with *n*-caproyl chloride and then rearranged by the Fries method to prepare the *n*-hexoylchlorocresols, which were finally reduced by the Clemmensen method to the *n*-hexylchlorocresols. The final products, after careful purification, were identical in physical properties and chemical analysis (Tables IV and V) with those obtained by the first method.

Experimental[9]

General Procedure for the Chlorination of Cresols.[10]—To 27 g. of melted *m*-cresol, 33.75 g. (20 cc.) of pure sulfuryl chloride was added slowly. The reaction started immediately at room temperature and gases of hydrogen chloride and sulfur dioxide evolved. By warming the reactants on a water-bath, the reaction was brought to completion. The product was washed with a cold solution of sodium carbonate, dried over fused calcium chloride, filtered and distilled. Nearly all of the product distilled over as pure 4-chloro-*m*-cresol, which boiled at 234 to 236°. It solidified on chilling. Recrystallized from ligroin, 4-chloro-*m*-cresol formed colorless prismatic needles, m. p. 66°. The yield amounted to 30 g., which was approximately 84% of the theoretical.

With *o*-cresol, an equally good yield was obtained of 4-chloro-*o*-cresol, which formed colorless needles, m. p. 48 to 49°; b. p. 220 to 225°. The product was purified by high vacuum distillation.

With *p*-cresol, a 77% yield was obtained of 2-chloro-*p*-cresol, which formed a colorless oil, b. p. 195 to 197°; d^{27}_4 1.1785; $n^{27}D$ 1.5200.

General Procedure for the Esterification of Cresols and Chlorocresols.—To 26.4 g. of chlorocresol (or a molecular equivalent of cresol) in 50 cc. of anhydrous carbon tetrachloride kept under reflux, 25 g. of *n*-caproyl chloride (b. p. 150–153°) was added slowly through the condenser. The reactants were refluxed until no hydrogen chloride gas evolved. The solvent, carbon tetrachloride, was removed by distillation. The residue was washed first with ice-water, then with cold dilute sodium carbonate solution and finally dried over fused calcium chloride. After filtration, the product was distilled at atmospheric pressure. The most constant boiling fraction was collected as the pure ester. The density and the refractive index were determined. The ester was redistilled in vacuum in an all-glass apparatus several times until the physical properties determined were constant. The final results are collected in Table I.

TABLE I

PHYSICAL PROPERTIES OF *n*-CAPROATES OF CRESOLS AND CHLOROCRESOLS

n-Caproates from	Boiling points, °C. (atmospheric pressure)	d^{25}_4	$n^{25}D$	Yield of product, %
o-Cresol	263–264	0.9786	1.4931	81.5
m-Cresol	280–283	0.9758	1.4934	77.0
p-Cresol	268–270	0.9758	1.4930	77.0
4-Chloro-*o*-cresol	280–283	1.0630	1.5059	75.0
4-Chloro-*m*-cresol	286–288	1.0604	1.5058	78.0
2-Chloro-*p*-cresol	283–285	1.0662	1.5038	85.0

General Procedure for the Conversion of Tolyl and Chlorotolyl *n*-Caproates to *n*-Hexoylcresols and *n*-Hexoylchlorocresols by Fries Rearrangement.—To 15 g. of chlorotolyl *n*-caproate (or a molecular equivalent amount of tolyl *n*-caproate) in a 250-cc. round-bottom flask, 13 g. of anhydrous aluminum chloride powder was slowly introduced. The mixture was heated under reflux in an oil-bath maintained at 140° for four hours. After cooling, 50 cc. of ice-water was added and then 50 cc. of concentrated hydrochloric acid. The mixture was carefully warmed under reflux to effect a complete decomposition of aluminum chloride. The rearrangement product was extracted from the mixture with benzene (50, 25, 25-cc. portions). The benzene extract was first washed with water and then with a cold solution of sodium carbonate. The extract was then dried with fused calcium chloride. After decantation and filtration the solvent was removed by distillation on a sand-bath. The residue was distilled in a high vacuum. The most constant boiling fraction was collected and redistilled in a high vacuum several times until the physical properties (density and refractive index) were constant. The final distillation was carried out in an all-glass apparatus. Results are tabulated in Table II.

General Procedure for the Conversion of *n*-Hexoylcresols and their Chloro Derivatives to *n*-Hexylcresols and *n*-Hexylchlorocresols by Clemmensen Reduction.—In a 250-cc. round-bottom flask joined by glass to a reflux condenser, 10 g. of mossy zinc was amalgamated with 1 g. of mercuric chloride by the procedure given by Gattermann-Wieland.[7] A toluene solution of the ketone (8 g. of *n*-hexoylchlorocresol or a molecular equivalent amount of *n*-hexoylcresol in 50 cc. of toluene) and an alcoholic solution of hydrochloric acid (20 cc. of concd. hydrochloric acid + 30 cc. of absolute ethyl alcohol) were added, alternately, drop by drop through the condenser to the zinc amalgam which had been prepared. Each reactant was divided into five portions of 10 cc. each. When all the reactants had been added, the mixture was refluxed on a sand-bath and

(8) Biltz, Hall and Blanchard, "Laboratory Methods of Inorganic Chemistry," 2nd ed., John Wiley and Sons, New York, N. Y., 1928, pp. 201–203.

(9) Preliminary experiments were carried out by Messrs. H. Kang, S. C. Fu, J. C. Chang, H. K. Han, C. C. Chang and S. C. Kao, senior students of Fu Jen University, from Aug. 15 to Sept. 12, 1940, in the laboratories of the Department of Pharmacology, P. U. M. C. Large amounts of materials were later collected by Messrs. Y. S. Lin, P. J. Chao and F. H. Chen, technical assistants of pharmacy, P. U. M. C. from Oct. 1, 1940, to April 1, 1941. Finally, the experimental data were carefully checked up by one of us (Peter P. T. Sah) from April 10 to June 10, 1941.

(10) (a) Vanino, "Praeparative Chemie," Bd. II, 1923, p. 422; (b) Dubois, *Z. Chem.*, 705 (1866); (c) Peratoner and Condorelli, *Gazz. chim. ital.*, **28**, I, 211–213 (1898); (d) Beilstein, "Handbuch d. org. Chem.," Bd. VI, 1923, pp. 359, 381.

TABLE II

PHYSICAL PROPERTIES OF *n*-HEXOYLCRESOLS AND *n*-HEXOYLCHLOROCRESOLS

Name of phenolic ketones	B. p., (reduced pressure) °C.	Mm.	d^{25}_4	$n^{25}D$	Yield of product, %
6-*n*-Hexoyl-*o*-cresol	131–132	1[11]	1.0072	1.5338	50.5[12]
6-*n*-Hexoyl-*m*-cresol	135–137	2[13]	1.0152	1.5339	85.0
6-*n*-Hexoyl-*p*-cresol	132–133	2[14]	1.0167	1.5315	62.0
4-Chloro-6-*n*-hexoyl-*o*-cresol	149–151	1	1.1128	1.5428	60.0
4-Chloro-6-*n*-hexoyl-*m*-cresol	152–154	1[15]	Pale yellow plates, m. p. 42–44°		76.0
2-Chloro-6-*n*-hexoyl-*p*-cresol	150–152	1	1.0876^{30}_4	$1.5396^{30}D$	62.0
	Pale-yellow needles, m. p., 25–27°.				

TABLE III

PHYSICAL PROPERTIES OF *n*-HEXYLCRESOLS AND *n*-HEXYLCHLOROCRESOLS

Name of phenols	Boiling points (reduced pressure) °C.	Mm.	d^{25}_4	$n^{25}D$	Yield of product, %
6-*n*-Hexyl-*o*-cresol	130–131	1[16]	1.0059	1.5297	70.0
6-*n*-Hexyl-*m*-cresol	132–133	1[17]	0.9964	1.5299	90.0
6-*n*-Hexyl-*p*-cresol	134–135	1[18]	0.9810	1.5232	70.0
4-Chloro-6-*n*-hexyl-*o*-cresol	140–142	1	1.1032	1.5404	90.0
4-Chloro-6-*n*-hexyl-*m*-cresol	150–152	2[19]	Colorless plates from 95% EtOH, m. p., 27–29°		80.0
2-Chloro-6-*n*-hexyl-*p*-cresol	137–139	1	1.0750	1.5381	75.0

TABLE IV

CARBON AND HYDROGEN CONTENTS OF TOLYL *n*-CAPROATES, 6-*n*-HEXOYLCRESOLS AND 6-*n*-HEXYLCRESOLS

Compounds	Formula	Hydrogen, % Calcd.	Found		Carbon, % Calcd.	Found	
o-Tolyl-*n*-caproate	$C_{13}H_{18}O_2$	8.80	8.87	8.90	75.68	75.63	75.72
m-Tolyl-*n*-caproate	$C_{13}H_{18}O_2$	8.80	8.95	9.00	75.68	75.65	75.71
p-Tolyl-*n*-caproate	$C_{13}H_{18}O_2$	8.80	8.94	8.94	75.68	75.78	75.87
6-*n*-Hexoyl-*o*-cresol	$C_{13}H_{18}O_2$	8.80	8.97	9.00	75.68	75.94	75.88
6-*n*-Hexoyl-*m*-cresol	$C_{13}H_{18}O_2$	8.80	8.93	9.01	75.68	75.61	75.85
6-*n*-Hexoyl-*p*-cresol	$C_{13}H_{18}O_2$	8.80	8.96	8.98	75.68	75.80	75.83
6-*n*-Hexyl-*o*-cresol	$C_{13}H_{20}O$	10.49	10.55	10.49	81.19	80.99	80.84
6-*n*-Hexyl-*m*-cresol	$C_{13}H_{20}O$	10.49	10.62	10.65	81.19	81.55	80.95
6-*n*-Hexyl-*p*-cresol	$C_{13}H_{20}O$	10.49	10.53	10.55	81.19	81.07	81.46

fresh concd. hydrochloric acid (5-cc. portions) was added at intervals until the zinc amalgam was almost completely dissolved. After cooling, the toluene layer was separated from the aqueous layer by means of a separatory funnel; the toluene solution of the product was dried over fused calcium chloride and filtered. The solvent, toluene, was then removed by distillation on a sand-bath. The residue was distilled in a vacuum. The most constant boiling fraction was collected and the physical properties determined. This product was redistilled several times in a high vacuum with an all-glass apparatus until the physical properties were constant. The final results are tabulated in Table III.

Chlorination of *n*-Hexylcresol to Monochloro-*n*-hexylcresol by Sulfuryl Chloride.—The procedure used for the preparation of monochloro-cresols was adopted with two modifications: (1) during chlorination, carbon tetrachloride was used as a solvent; (2) after chlorination, the product was distilled in a high vacuum instead of at atmospheric pressure since it had a high boiling point. The yield was from 60 to 65%. From the physical properties and the chemical analysis (chlorine content) it is apparent that these products were identical with those obtained by Clemmensen's reduction of the corresponding *n*-hexoylchlorocresols.

Toxicity of *n*-Hexylcresols and *n*-Hexylchlorocresols.—Acute toxicity studies in mice and rats, by subcutaneous injection and gastric administration, respectively, revealed that chlorination appreciably lessened the toxic effects of *n*-hexylcresols. For mice, the unchlorinated meta compound killed half of the animals given 1.8 cc. per kilo while after chlorination the product killed at 4 cc. per kilo. The unchlorinated para compound was lethal for half of the mice

(11) Described by Coulthard, Marshall and Pyman, *J. Chem. Soc.* (London), 280–291 (1930), as 3-*n*-hexoyl-*o*-cresol, b. p. 152–154° at 15 mm.

(12) A considerable amount of an isomer, 4-*n*-hexoyl-*o*-cresol, was formed, which distilled at 180–182° at 2 mm. and crystallized from benzene as white plates, m. p. 79–80° (also described by Coulthard, *et al.*).

(13) Described by Coulthard, *et al.*, as 4-*n*-hexoyl-*m*-cresol, b. p. 161–164° at 15 mm.

(14) Described by Coulthard, *et al.*, as 3-*n*-hexoyl-*p*-cresol, b. p. 150–152° at 15 mm.

(15) Described by Hartman and Schelling as a solid mass.

(16) Described by Coulthard, Marshall and Pyman as 3-*n*-hexyl-*o*-cresol, b. p. 139–141° at 15 mm., m. p. 8°.

(17) Described by the above authors as 4-*n*-hexyl-*m*-cresol, b. p. 147–149° at 15 mm.; m. p. 17°.

(18) Described by the above authors as 3-*n*-hexyl-*p*-cresol, b. p. 148–150° at 15 mm.; m. p. 30°.

(19) Described by Hartman and Schelling as a colorless oil, b. p. 148–150° in high vacuum, which crystallized to a white mass in the cold.

given 2.3 cc. per kilo; after chlorination, the product killed at 8.6 cc. per kilo. The unchlorinated ortho isomer was lethal for half of the animals at 4.0 cc. per kilo; after chlorination the product was slightly less toxic at 4.5 cc. per kilo. For rats, the order of toxicity was similar except that the unchlorinated para compound was most toxic. Detailed pharmacological reports will be published elsewhere.[20]

TABLE V

CHLORINE CONTENTS OF CHLOROTOLYL *n*-CAPROATES, 6-*n*-HEXOYLCHLOROCRESOLS AND 6-*n*-HEXYLCHLOROCRESOLS

Compounds	Formula	Chlorine, % Calcd.	Found	
4-Chloro-*o*-tolyl-*n*-caproate	$C_{13}H_{17}O_2Cl$	14.73	14.94	14.85
4-Chloro-*m*-tolyl-*n*-caproate	$C_{13}H_{17}O_2Cl$	14.73	14.89	14.91
2-Chloro-*p*-tolyl-*n*-caproate	$C_{13}H_{17}O_2Cl$	14.73	14.62	14.87
4-Chloro-6-*n*-hexoyl-*o*-cresol	$C_{13}H_{17}O_2Cl$	14.73	14.96	14.85
4-Chloro-6-*n*-hexoyl-*m*-cresol	$C_{13}H_{17}O_2Cl$	14.73	14.95	14.84
2-Chloro-6-*n*-hexoyl-*p*-cresol	$C_{13}H_{17}O_2Cl$	14.73	14.64	14.70
4-Chloro-6-*n*-hexyl-*o*-cresol	$C_{13}H_{19}OCl$	15.64	15.57	15.60
4-Chloro-6-*n*-hexyl-*m*-cresol	$C_{13}H_{19}OCl$	15.64	15.56	15.58
2-Chloro-6-*n*-hexyl-*p*-cresol	$C_{13}H_{19}OCl$	15.64	15.67	15.61

(20) Hu and Anderson, paper in press.

Summary

Detailed data regarding the methods used for the preparation of the isomeric *n*-hexyl- and *n*-hexoylcresols as well as their monochloro derivatives and their properties are described.

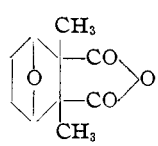
PEIPING, CHINA RECEIVED SEPTEMBER 13, 1941

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

The Structure of Cantharidine and the Synthesis of Desoxycantharidine

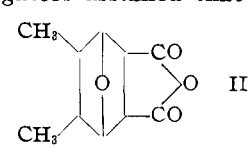
BY R. B. WOODWARD AND R. B. LOFTFIELD

Cantharidine, the active principle of *cantharis vesicatoria*, has been assigned the structure I on the basis of analytic evidence, much of which was amassed in a series of brilliant investigations by Gadamer and his collaborators,[1a,b,c,d] although the substance has attracted the attention of many chemists since its isolation in 1810 by Robiquet.[2]



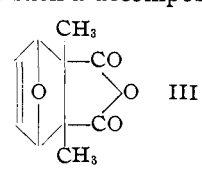
I

The decision in favor of I over the alternate formulation II, which may likewise be accommodated with the bulk of the earlier evidence, was made largely as a result of the work of von Bruchhausen and Bersch,[3] who obtained small amounts of dimethylmaleic anhydride on passing cantharidine over palladium-asbestos at > 280°. These investigators assumed that the anhydride



II

was formed by an inverse Diels–Alder reaction of the hypothetical dehydrocantharidine III. The assumption that such a decomposition would take



III

place is an eminently reasonable one, in view of the ready reversibility of the furan–maleic anhydride reaction,[4] and the failure of numerous attempts to add dimethylmaleic anhydride to furan to obtain III.[3,4] However, we feel that the experiments of von Bruchhausen and Bersch, while pointing toward structure I for cantharidine, do not afford unequivocal proof of this structure. Applying to formula II the breakdown mechanism adduced by these authors, the initial products would be 3,4-dimethylfuran and maleic anhydride. Under the conditions of the experiment it is not inconceivable that partial oxidation of 3,4-dimethylfuran could account for the small amounts of dimethylmaleic anhydride observed.[5]

Thus, while the analytic evidence indicates that cantharidine has the structure I, no synthetic

(1) (a) Danckwortt, *Arch. Pharm.*, **252**, 632 (1914); (b) Gadamer, *ibid.*, **252**, 636 (1914); (c) Rudolph, *ibid.*, **254**, 454 (1916); (d) Gadamer, *ibid.*, **252**, 623, 660 (1914), and many other papers.

(2) Robiquet, *Ann. chim.* [1] **76**, 307 (1810).

(3) Von Bruchhausen and Bersch, *Arch. Pharm.*, **266**, 697 (1929).

(4) Diels and Alder, *Ber.*, **62**, 554 (1929).

(5) *Cf.* Milas and Walsh, THIS JOURNAL, **57**, 1389 (1935), for the conversion of furan to maleic anhydride under somewhat comparable conditions.