mately $^1/_2$ the potency of the ring system III bearing the same side chain.[20,21]

EXPERIMENTAL

N-Dimethylaminopropyl-6,6-dimethyl-3-azabicyclo[3:1:0]-hexane-2,4-dione. A total of 16.8 g. (0.15 mole + 10% excess) of dimethylaminopropylamine was added to 21 g. (0.15 mole) of caronic anhydride contained in a 50-ml. round bottom flask. After the immediate exothermic reaction subsided, the reaction mixture was stirred and heated gently until a homogeneous melt was obtained. The temperature was slowly raised to 180–190° and maintained for 2 hr. The imide was isolated by distillation *in vacuo* to yield 28 g., 83%, of product, b.p. 101–111° at 0.3 mm.

The *hydrochloride* was prepared in isopropyl alcohol with excess alcoholic HCl and precipitated with ether. On recrystallization from isopropyl alcohol–ether it melted at 162–163°.

The *methiodide* was prepared in ethyl acetate with a slight excess of methyl iodide and recrystallized from isopropanol-ether, m.p. 237–238°.

N-Dimethylaminopropyl-6,6-dimethyl-3-azabicyclo[3:1:0]-hexane. A solution of 12 g. (excess) of lithium aluminum hydride in 800 ml. of anhydrous ether was prepared in a 2-liter, 3-necked reaction flask fitted with a stirrer, dropping funnel, and condenser, and protected from atmospheric moisture. A solution of 22.4 g. (0.1 mole) of 3-dimethylaminopropyl-6,6-dimethyl-3-azabicyclo[3:1:0]hexane-2,4-dione in 400 ml. of anhydrous ether was added dropwise with stirring at such a rate as to just maintain reflux of the ether. The reaction mixture was stirred an additional 2 hr. and then decomposed by dropwise addition of water. After an hour of additional stirring the inorganic precipitate was filtered and washed with 3 portions of ether, which were combined with the filtrate and dried over anhydrous sodium sulfate. The ether was stripped off and the residue distilled under reduced pressure to yield the base, 18 g., 91%, b.p. 104–106° at 14 mm.

The *hydrochloride* was prepared in the usual manner, m.p. 230–231°.

The *dimethiodide* was prepared by refluxing the base dissolved in absolute alcohol with a 10% excess of methyl iodide for several hours, m.p. 227–228°.

All of the compounds were prepared as outlined in the above examples except the *dimethiodide of N-dimethylaminopropyl-6,6-dimethyl-3-azabicyclo[3:1:1]heptane.* In this case, the base dissolved in methanol was heated in a bomb tube for 4 hr. with a 10% excess of methyl iodide. The product was washed out of the bomb tube, precipitated with ether and recrystallized several times from alcohol ether, m.p. 231°.

RADNOR, PA.

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(20) W. E. O'Malley, G. W. Haemmerli, L. M. Rice, and C. F. Geschickter, *J. Am. Pharm. Assoc. Sci. Ed.*, **47**, 263 (1958).

(21) This compound is known as Wy-1395, Trimethidinium, and OSTENSIN.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, DIAMOND ALKALI COMPANY]

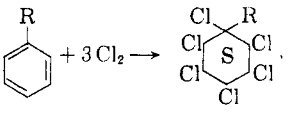
The Addition-Chlorination of Phenol[1]

IRVING ROSEN AND JOHN P. STALLINGS

Received April 28, 1959

Benzene derivatives with strong electron releasing groups such as phenol have not been addition-chlorinated in the past because of the ease with which they undergo substitution. The modification of the electron releasing properties of the hydroxy group in phenol by the use of electron withdrawing groups attached to the oxygen atom permits addition-chlorination to take place readily. Phenyl haloacetates were addition-chlorinated in good yields. Hydrolysis of the addition products suggests that the major stable product from the addition-chlorination of phenol is 2,4,6-trichlorophenol.

The literature contains descriptions of the addition-chlorination of several substituted benzenes. The most comprehensive study of these reactions was made by T. van der Linden.[2] The reactions he studied are summarized below. The most recent work reported on this reaction with substituted benzenes dwelled upon the effect of reaction conditions on the product yields.[3,4]



where R = F, CN, COCl, COOH, NO_2, CCl_3, $CHCl_2$, CH_2Cl, CH_3

A common property of these substituted benzenes is that they do not readily undergo chlorine substitution without the presence of an acid catalyst. Under conditions favorable for addition-chlorination, the addition reaction can take place instead of the substitution reaction. In some cases both reactions have occurred. Some of the major products isolated from reactions of this sort have been substituted by chlorine and then addition-chlorinated.

Among the compounds missing from the above are those which contain strong electron releasing groups and which readily undergo substitution-chlorination, even in the absence of an acid catalyst, *i.e.*, compounds such as phenol and aniline.

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(1) Presented before the Organic Division at the 135th Meeting of the American Chemical Society, Boston, Mass., April 10, 1959.

(2) T. van der Linden, *Rec. trav. chim.*, **53**, 45 (1934); **53**, 703 (1934); **55**, 282 (1936); **57**, 342 (1938); **57**, 1075 (1938).

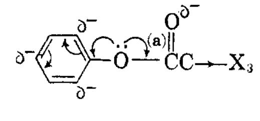
(3) D. E. Harmer, *AECU*-3077 (1955).

(4) I. Rosen and J. P. Stallings, *Ind. & Eng. Chem.*, **50**, 1511 (1958).

It was the purpose of this work to addition-chlorinate phenol, or a phenol derivative, and to determine the nature of the product of the addition-chlorination of phenol.

In order to achieve the addition-chlorination of phenol, it appeared necessary either to conduct the chlorination at very low temperatures, or to so modify the phenolic OH group that the tendency of the molecule to undergo substitution would be considerably curtailed. The first alternative did not appear attractive because of the probable low reaction speeds at the low temperatures required. Furthermore, if low-temperature addition had taken place, a *gem* chlorohydrin, II, would have been formed, the isolation of which did not appear possible, because of the instability of such structures. For these reasons, the latter alternative appeared to offer the best route.

To modify the activating influence of the phenolic OH group, it is necessary to reduce its electron donating properties towards the benzene ring. It seemed that this could be accomplished by combining the phenolic oxygen atom with groups exerting a negative inductive effect. A strong inductive effect by this new group upon the electrons surrounding the phenolic oxygen atom would reduce their contribution towards activation of any positions on the benzene ring. In the case of phenol, it is known that the *ortho-para*-orienting power is considerably reduced after it has been converted to the acetate.[5] The use of the haloacetates should diminish this *ortho-para*-orienting power even more by virtue of the added inductive effect of the halogens upon the unshared electrons on the oxygen. Because of the displacement (a), the unshared electrons on the oxygen are less available for activation of the aromatic nucleus. Consequently, the haloacetate group is less powerfully *ortho-para* directing than the unsubstituted hydroxy group and should be less directing than the acetate group. The deactivation of the nucleus reduces the rate of the substitution-chlorination reaction and should permit the addition-chlorination to take place more readily under favorable conditions.



The first strong electron withdrawing group used to deactivate the phenol was the trichloroacetyl radical. The phenyl trichloroacetate was prepared by conventional means. The mixture of phenyl trichloroacetate, together with CCl_4 and the theoretical amount of chlorine for addition was sealed in a borosilicate glass tube and exposed to ultraviolet irradiation for 22 hr. The phenyl trichloroacetate was readily addition-chlorinated in quantitative yields. The first evidence for the complete addition chlorination was afforded by the absence of the chlorine color in the reaction vessel and by the absence of HCl when the reaction tube was opened. The ease with which the addition-chlorination reaction took place and the quantitative yields were obtained was very gratifying. The crude reaction product was many times found pure enough for use in other reactions.

The structure of the 1,2,3,4,5,6-hexachlorocyclohexyl trichloroacetate was confirmed by infrared analyses. It was suspected that the product could be a mixture of unsaturated chlorinated products and overchlorinated products which fortuitously gave the correct analysis. The spectrogram contained no evidence of benzene unsaturation or aliphatic unsaturation, resembled that of the 1,2,3,-4,5,6-hexachlorocyclohexanes to a modified extent, and contained strong bands supporting the acetate group.

After it was found that phenyl trichloroacetate was readily addition-chlorinated, several other phenol esters were prepared and investigated in this reaction. Table I summarizes the results obtained with the phenyl haloacetates. The wide range in the boiling points of the products in Table I is probably due to the number of stereoisomers present. Elemental and infrared analyses of various fractions of the same product showed little variation.

To determine if the halogen substituent in the haloacetate were necessary for the addition-chlorination, an attempt was made to carry out the addition reaction with phenyl acetate. The product consisted of a mixture of substitution-chlorinated materials, and no addition-chlorinated material. Thus it appears that the additional deactivating influence of the halogen ester is necessary to obtain the desired reaction.

Some esters other than the haloacetates were found to permit addition-chlorination. Table II summarizes the results of the addition chlorination of diphenyl carbonate and triphenyl phosphate. The analyses of these materials indicate that the products were not completely addition-chlorinated. The products, however, were difficult to purify because of a tendency to decompose during heating. This is not surprising in view of the steric strain which is probably present in these crowded molecules. The infrared spectra of the compounds contained only weak bands for benzene unsaturation and many bands supporting the saturated structure.

To determine the product of the addition-chlorination of phenol, I was hydrolyzed by dilute acid under mild conditions. The product of the acid hydrolysis consisted of a 90% yield of 2,4,6-trichlorophenol (V).

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(5) C. K. Ingold, *Structure and Mechanism in Organic Chemistry,* Cornell University Press, Ithaca, N. Y., 1953, p. 239.

TABLE I

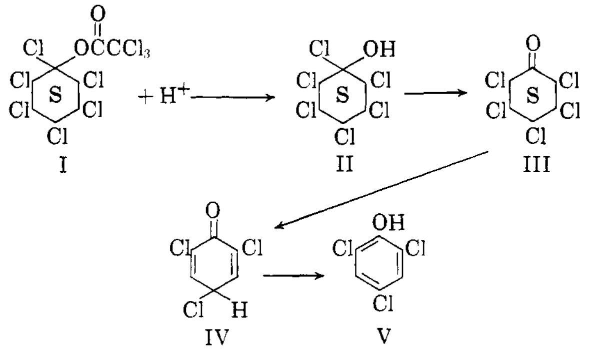
ADDITION-CHLORINATION OF PHENYL HALOACETATES

Phenyl haloacetate	Products				Analyses, %					
					Calculated			Found		
	B.p., °C./mm.	n_D^{25}	Yield, %	Formula	C	H	Cl	C	H	Cl
$C_6H_5OCOCCl_3$	160–164/0.3–0.4	1.5532	90	$C_8H_5O_2Cl_9$	21.25	1.11	70.5	21.15	1.16	70.6
$C_6H_5OCOCHCl_2$	162–175/0.7		79	$C_8H_6Cl_8O_2$	22.95	1.44	67.8	22.58	1.77	66.8
$C_6H_5OCOCH_2Cl$	166–172/1.2	1.5558	43	$C_8H_5Cl_7O_2$	25.05	1.84	64.9	25.00	1.92	65.6
	172–176/1.2		51					23.64	1.68	65.1
$C_6H_5OCOCF_3$	120–126/1.1	1.4910	65	$C_8H_5F_3Cl_6O_2$	23.82	1.25	52.8	23.22	1.27	53.3
p-$ClC_6H_4OCOCCl_3$	180–192/1.0	1.5624	76	$C_8H_4Cl_{10}O_2$	19.73	0.83	72.8	19.79	0.93	72.3

TABLE II

ADDITION-CHLORINATION OF DIPHENYL CARBONATE AND TRIPHENYL PHOSPHATE

Starting Material	Products		Formula	Analyses, %					
				Calculated			Found		
	M.p., °C.	Yield, %		C	H	Cl	C	H	Cl
Diphenyl carbonate	84–90°	47	$C_{13}H_{10}Cl_{12}O_3$	24.4	1.6	66.5	25.3	1.7	63.4
Triphenyl phosphate	120° (dec.)	62	$C_{18}H_{15}Cl_{18}PO_4$	22.4	1.6	66.2	26.2	2.2	60.6



The proposed explanation for the formation of the 2,4,6-trichlorophenol rather than other isomers is represented by the above sequence of steps. Initially, the ester I should be hydrolyzed to the *gem* chlorohydrin, II, which is the product of the addition chlorination of phenol. The *gem* chlorohydrin, II, then undergoes dehydrochlorination to the 2,3,4,5,6-pentachlorocyclohexanone, III. The *beta* chlorine atoms of ketones are easily eliminated. It is postulated that III preferentially eliminates the *beta* chlorine atoms and forms a dienone such as IV which rapidly undergoes the dienone-phenol rearrangement to the product, V. An inference of the results is that if phenol were addition-chlorinated to II, II would probably undergo the same dehydrochlorination path and sequence of steps and yield V as the major stable product.

EXPERIMENTAL

Preparation of the Phenyl Haloacetates. Most of the phenyl haloacetates were prepared in better than 80% yields by refluxing equimolar quantities of the phenol and the appropriate acid chloride until the evolution of HCl ceased. The product was then purified by distillation or recrystallization.

Phenyl trichloroacetate. B.p. 122°/14 mm. and 137–138°/24 mm.; n_D^{20} 1.5233 (lit. b.p. 125–126°/14 mm.[6]).

Phenyl dichloroacetate was recrystallized from hexane, m.p. 48.5–49.5° (lit. m.p. 48°[7]).

Phenyl chloroacetate. B.p. 140–141°/31 mm. (lit. b.p. 155°/65 mm.[8]).

p-Chlorophenyl trichloroacetate. B.p. 170–172°/34 mm. and 108/110°/0.8–0.9 mm. Bhargava and Sen[9] reported a b.p. of 94–98°/4 mm. Because of the discrepancy in boiling points, our material was subjected to infrared and elemental analyses. The infrared spectrum showed a strong absorption band at 1200 cm.$^{-1}$ plus the carbonyl band to support the acetate group. There was also support for 1,4 substitution in the benzene ring, n_D^{25} 1.5383.

Anal. Calcd. for $C_8H_4Cl_4O_2$: C, 35.0; H, 1.47; Cl, 51.6. Found: C, 34.9; H, 1.70; Cl, 51.2.

Phenyl trifluoroacetate was prepared in 83% yield by refluxing phenol with trifluoroacetic anhydride at 100–120° for 2 hr., b.p. 146.5–147° (lit. b.p. 146.5–147.0°[10]).

2,4,6-Trichlorophenyl trichloroacetate was prepared by refluxing the mixture of the sodium salt of 2,4,6-trichlorophenol with trichloroacetyl chloride in dry dioxane for 2.5 hours. Evaporation of the dioxane and distillation of the residue gave the product, b.p. 110–112°/0.09 mm., n_D^{25} 1.5597, in 40% yield.

Anal. Calcd. for $C_8H_2Cl_6O_2$: C, 28.1; H, 0.58; Cl, 62.0. Found: C, 28.6; H, 0.87; Cl, 61.5.

Addition Chlorination of the Phenol Esters. The esters were generally addition-chlorinated by irradiating the ester and liquid chlorine, with or without CCl_4 as a solvent, in a sealed borosilicate glass tube with a 15 watt General Electric Company black light fluorescent lamp (catalogue no. F15T8-BL). The following examples illustrate the method.

Preparation of 1,2,3,4,5,6-hexachlorocyclohexyl trichloroacetate (I). In a thick-walled borosilicate glass tube of 2.5 cm. i.d. were placed 24.0 g. (0.10 mole) of phenyl trichloroacetate and 21.4 g. (0.30 mole) of chlorine. The tube was sealed and placed adjacent to a black light fluorescent lamp for 22 hr. When the tube was opened, no HCl was detected. After venting, the gain in weight of the non-volatile contents

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(6) W. Kuster and G. Koppenhoffer, *Ber.*, **60**, 1778 (1927).

(7) H. Crompton and P. M. Triffitt, *J. Chem. Soc.*, **119**, 1874 (1921).

(8) K. Fries and W. Pfaffendorf, *Ber.*, **43**, 214 (1910).

(9) P. M. Bhargava and A. B. Sen, *J. Sci. Food and Agr.*, **1**, 178 (1950).

(10) R. F. Clark and J. H. Simons, *J. Am. Chem. Soc.*, **75**, 6306 (1953).

of the tube corresponded to complete addition of the chlorine. The reaction product was a nearly colorless, dense, highly viscous liquid. Distillation gave about 90% of the theoretical quantity of product, b.p. 160–164°/0.4 mm., d_{20}^{20} 1.745. Calcd.: Mr_D^{20} 82.40. Found: 82.98.

Anal. Calcd. for $C_8H_5O_2Cl_9$: C, 21.25; H, 1.11; Cl, 70.5. Found: C, 21.15; H, 1.16; Cl, 70.6.

Because the reaction product was very viscous, some product was held up in parts of the distillation apparatus, lowering the yield. The crude undistilled reaction mixture was analyzed.

Anal. Found: C, 21.03; H, 1.02; Cl, 71.0.

Preparation of bis(1,2,3,4,5,6-hexachlorocyclohexyl) carbonate. In a thick-walled borosilicate glass tube were placed 10.7 g. (0.050*M*) of diphenyl carbonate, 31.6 g. (0.44*M*) of chlorine, and 18.0 ml. of carbon tetrachloride. The tube was sealed and irradiated by a black light fluorescent lamp for 17 hr. After the tube was vented, there was a 29.6 g. weight gain in the nonvolatile materials. The product was dissolved in methanol, precipitated by the addition of water, and rapidly filtered and dried. In the first crop, 15.0 g. of product was obtained, m.p. 84–90°.

Anal. Calcd. for $C_{13}H_{10}Cl_{12}O_3$: C, 24.4; H, 1.58; Cl, 66.5. Found: C, 25.3; H, 1.7; Cl, 63.4.

Subsequent materials which were precipitated were lower melting and gave greater deviations from the theoretical values in the elemental anaylsis.

Hydrolysis Experiments. The acid hydrolysis of I was effected by stirring a mixture of 15.0 g. (0.0332*M*) of I, 60 ml. of dioxane, 30 ml. of conc. HCl, and 60 ml. of water at reflux for one hour. The hydrolysis mixture was saturated with salt and the organic material separated by extraction with chloroform. After evaporation of the chloroform, distillation of the residue gave 8.3 g. of one fraction, b.p. 120–124°/39 mm. and 1.4 g. of 2,4,6-trichlorophenol, identified by elemental analysis and a mixed m.p. with an authentic sample. The first fraction was a binary mixture (apparently azeotropic) containing about an equimolar ratio of 2,4,6-trichlorophenol to trichloroacetic acid. The total amount of 2,4,6-trichlorophenol obtained was 5.9 g., or a 90% yield.

The hydrolysis of 0.08*M* of the addition-chlorinated phenyl trifluoroacetate in dioxane-water at 10–25° followed by chloroform extraction and distillation of the extract gave a 70% yield of the 2,4,6-trichlorophenol. The phenol was identified by a mixed melting point; benzoate, m.p. 74–75°.

PAINESVILLE, OHIO

[FROM THE DEPARTMENT OF BACTERIOLOGY, THE UNIVERSITY OF KANSAS]

Adduct Formation between Chloroacetone and *N'*-Alkyl Substituted Pyridine Bases and Its Biological Significance[1-3]

J. M. AKAGI* AND D. PARETSKY

Received April 29, 1959

The reaction involving adduct formation between DPN[4] and various carbonyl compounds have been extensively studied by Burton and Kaplan.[5,6] The mechanism for this reaction, proposed by these workers, involves a prior ionization of a proton from the carbon alpha to the carbonyl carbon, resulting in the formation of a negatively charged molecule. This is followed by an addition reaction with the positively-charged 4-carbon of the pyridinium moiety of DPN. The reaction can be followed by the appearance of a characteristic maximum absorption for that particular adduct. In this report will be presented results of adduct formation obtained between chloroacetone and *N'*-alkyl substituted pyridinium bases. When *N'*MeN is caused to react with chloroacetone in basic solutions, the formation of an adduct is apparent by the formation of a new maximum in the 360 mμ region of the absorption spectrum. Substituting the carbamoyl for a carboxaldehyde group resulted in a pyridinium compound (*N'*MePyAl), which in smaller quantities was capable of reacting with chloroacetone at a rate faster than *N'*MeN. When, instead of aldehyde, an acetyl group was attached to the pyridine ring, a compound was obtained which was intermediate between *N'*MeN and *N'*MePyAl in adduct-forming abilities. Table 1 summarizes these findings.

In order to determine whether or not the group attached to the positive nitrogen atom influenced adduct formation, the carbon density around the ring nitrogen was increased by preparing the ethyl, isopropyl, and tertiary butyl derivatives of the pyridine bases. Rate studies comparing adduct formation between *N'*-methyl and the larger alkyl derivatives showed that with increasing carbon density around the ring nitrogen decreasing rates of addition reactions were obtained. This can be seen in Fig. 1 where the reactivity of *N'*MePyAl

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(*) Present address: Dept. of Microbiology, Western Reserve University.

(1) Taken from a thesis submitted by J. M. Akagi in partial fulfillment of the requirement for the degree of Doctor of Philosophy.

(2) This investigation was supported in part by the American Cancer Society, Institutional Grant 57 M 578-G, and by the University of Kansas General Research Fund.

(3) This report was presented at the Missouri Branch, Society of American Bacteriologists' Meeting in Manhattan, Kansas, in April 1958, and at the Midwest Regional Biochemistry Meeting in Lawrence, Kansas, October 1958.

(4) The following abbreviations will be employed in this paper: diphosphopyridine nucleotide (oxidized), DPN; *N'*-methylnicotinamide, *N'*-MeN; *N'*-ethylnicotinamide, *N'*-EtN; *N'*-isopropylnicotinamide, *N'*iPrN; *N'*-methyl-3-acetylpyridine, *N'*MeAP; *N'*-methyl-pyridine-3-carboxaldehyde, *N'*MePyAl; *N'*-tertiary butylpyridine-3-carboxaldehyde, *N'*-*tert*-BuPyAl.

(5) R. M. Burton and N. O. Kaplan, *J. Biol. Chem.*, **206**, 283 (1954).

(6) N. O. Kaplan, *Record of Chem. Prog.*, **16**, 177 (1955).