Reactions of *tert*-Butyl Hypochlorite. IV.¹ The Reaction between *tert*-Butyl Hypochlorite and Benzamides

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Received June 26, 1962

When benzamide and its derivatives are treated with *tert*-butyl hypochlorite, the products obtained are nearly always N-chlorobenzamides; only two cases of nuclear chloro compounds being formed were noted. Two main classes of N-chlorobenzamides can be distinguished, the distinction being based on whether they can undergo rearrangement to nuclear chlorobenzamides or not.

The N-chlorination of benzamide has been carried out using various reagents: bleaching powder,² gaseous chlorine,^{3a,b} sodium hypochlorite,⁷⁻¹³ and ethyl chlorocarbamic ester.¹⁴

tert-Butyl hypochlorite was first used as a Nchlorinating agent by Clark¹⁵ and later by Israelstam,¹⁶ Chalsty and Israelstam¹⁷ and by Zimmer and Audrieth¹⁸ to prepare N-chloroamides. Chalsty and Israelstam also showed that tert-butyl hypochlorite reacted with anilides to give either N-chloroanilides (in the presence of borax)¹⁹ or nuclear chloroanilides (in the absence of borax).¹⁶

Since the nuclear chlorination of benzamide and its derivatives has not been reported and in continuation of the work on *tert*-butyl hypochlorite as a chlorinating agent in this laboratory, a study was made of the action of *tert*-butyl hypochlorite on methanolic solutions of substituted benzamides. The reaction mixture on being allowed to stand overnight gave in most cases good yields of Nchlorobenzamides. As a check, some of the latter were prepared using sodium hypochlorite solution according to the method of Hauser and Renfrow.²⁰

On treatment with alkali the N-chlorobenzamides, as was to be expected, underwent the Hofmann reaction with the formation of the corresponding amine.

These compounds were also treated with hydro-

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chloric acid in order to bring about their rearrangement to nuclear chloroamides. A study of these results showed that two classes of N-chlorobenzamides could be distinguished: (a) those which did not rearrange in acid solution and (b) those which did rearrange in acid solution. On the basis of these results and the reaction of the parent benzamide with tert-butyl hypochlorite, it was possible to classify benzamides into four groups: (i) amides such as benzamide itself and its methyl, chloro, and nitro derivatives which are not strongly activated towards nuclear substitution and hence give N-chloroamides which do not rearrange in acid solution; (ii) methoxybenzamides which are activated and give N-chloroamides which rearrange quite readily; (iii) amides which give only nuclear chloroamides derived from amides with very strongly activating hydroxyl and amino groups; (iv) amides containing inactive groups, e.g., carboxyl, which did not react at all with tertbutyl hypochlorite.

(i) Amides Giving N-Chloroamides which Did Not Rearrange in Acid Solution.—Table IA gives a list of amides which fall into this group. When they were treated with hydrochloric acid they decomposed into free chlorine and the original amide, and no trace of any nuclear chloroamide could be found.

All the N-chloroamides prepared were white crystalline compounds that liberated iodine from acidified potassium iodide solution. Each melting point was usually below that of the corresponding amide.

(ii) Amides giving N-Chloroamides which Did Rearrange in Acid Solution into Nuclear Chloroamides.—When 2-methoxy- and 4-methoxybenzamides were chlorinated in methanol solution with *tert*-butyl hypochlorite, a mixture of N-chloroand the respective 5- and 3-chloroamides was obtained; Table IB. Separation was effected by the difference of solubility in methanol, but the yields were low.

However, when the above methoxybenzamides were chlorinated in the presence of borax, the respective N-chloroamides were obtained in good yield. When these were allowed to stand overnight in the presence of either hydrochloric acid or sulfuric acid, rearrangement took place and the respective

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		TUDDE				
N-Chloro	Molecular	Yield,	Chlorine		M.p., °C	
derivative of	formula	%	Caled.	Found	Obad.	Lit.
		Α				
Benzamide		71			117-118	117-11816
2-Methylbenzamide	C ₈ H ₈ ONCl ^a	45	20.94	20.80	88-89	Not reported
4-Methylbenzamide	C ₈ H ₈ ONCl	70	20.94	20.83	147	Not reported
2,4-Dimethylbenzamide	C ₉ H ₁₀ ONCl	56	19.34	19.24	143	Not reported
4-Nitrobenzamide	C7H5O3N3Clb	61	17.70	17.62	200 - 202	Not reported
3-Nitrobenzamide	$C_7H_8O_3N_2Cl$	55	17.70	17.60	184	183-18412
3,5-Dinitrobenzamide	$C_7H_4O_8N_8Cl$	57	14.45	14.41	168	Not reported
2-Chloro-4-nitrobenzamide	$C_7H_4O_8N_2Cl_2$	90	15.10	15.06	184-185	Not reported
4-Chlorobenzamide	$C_7H_8ONCl_2$	84	18.68	18.62	194-195	Not reported
2-Chlorobenzamide	$C_7H_5ONCl_2$	81	18.68	18.61	105 - 106	Not reported
2-Bromobenzamide	C7H5ONClBr	75	15.14	15.10	151 - 152	Not reported
2-Iodobenzamide	C7H5ONCII	60	12.61	12.59	176 - 177	Not reported
3-Chlorobenzamide	C7H5ONCl3	76	18.68	18.57	119 - 120	Not reported
3,4-Dichlorobenzamide	C7H4ONCl	72	15.81	15.63	156 - 158	Not reported
2-Methyl-3,5-dinitrobenz-	$C_8H_6N_4O_5Cl^b$	65	13.68	13.49	199 - 200	Not reported
amide						
Phthalamide	$C_8H_7O_2N_2Cl$	66	17.88	17.70	187 - 188	Not reported
Phthalimide	C₃H₄O₂NCl	70	19.52	19.51	184 - 185	181–184 ¹⁸
1-Naphthamide	C ₁₁ H ₈ NOCl	54	17.27	16.99	125 - 126	Not reported
2-Naphthamide	C ₁₁ H ₈ NOCl	52	17.27	17.00	137 - 138	Not reported
3-Methoxybenzamide	$C_8H_8O_3NCl$	64	19.14	19.10	165 - 166	Not reported
		в				
2-Methoxybenzamide	$C_8H_sO_2NCl$	67	19.14	19.10	128	Not reported
4-Methoxybenzamide	$C_{8}H_{8}O_{2}NCl$	68	19.14	18.93	142 - 143	Not reported
a Comment alling of forement distingthe and athem	Crystallized from mothenel					

TABLE I

^a Crystallized from diethyl ether. ^b Crystallized from methanol.

5-chloro-2-methoxybenzamide and 3-chloro-4-methoxy-benzamide were isolated.

(iii) Amides which Gave Only Nuclear Chloroamides.—Salicylamide and its amino analog, anthranilamide, were two of the amides investigated which underwent nuclear chlorination.

When a solution of salicylamide in methanol was treated with *tert*-butyl hypochlorite, 5-chlorosalicylamide was obtained in almost quantitative yield. In the presence of either borax or sodium acetate 5-chlorosalicylamide was again formed but in smaller yield. No reaction took place in the presence of sodium hydroxide.

It is interesting to note that the chlorine atom enters the ring *para* to the hydroxy group. This property of a 2-hydroxy group has been previously reported. Ginsberg²¹ showed that when salicylaldehyde was chlorinated with *tert*-butyl hypochlorite the chlorine atom entered the *para* position to the hydroxyl. Likewise Chalsty and Israelstam¹⁹ showed that salicylanilide gave 2-hydroxy-5-chlorosalicylanilide.

Anthranilamide in methanol and methanol-borax solutions with *tert*-butyl hypochlorite gave only a tar. The addition of *tert*-butyl hypochlorite caused charring to take place even when the solution was cooled to below 5° .

In glacial acetic acid solution, however, it gave 3,5-dichloroanthranilamide. Eller and Klemm²² prepared 5-chloroanthranilic acid, in 50% yield, by treating an ethereal solution of anthranilic acid with sulfuryl chloride. The fact that a dichloro derivative of anthranilamide is obtained whereas

anthranilic acid only yields a monochloro derivative indicates that the carboxyl group has a greater deactivating effect than the amide group. Ginsberg²¹ also noted the deactivating influence of the carboxyl group present in aldehydes when the latter were treated with *tert*-butyl hypochlorite.

(iv) Amides which Did Not React with tert-Butyl Hypochlorite.—Phthalamic acid was found to be unaffected by the hypochlorite. Various solvents were used but in all cases the unchanged phthalamic acid was obtained. This is further evidence of the deactivating effect of the carboxyl group.

The N-chlorination of the benzamides by means of *tert*-butyl hypochlorite probably occurs by a direct SN2 displacement of the chlorine by the electron pair of the nitrogen



In regard to the few cases where nuclear chlorination occurs, the N-chlorobenzamide which is first formed rearranges in the presence of either hydrochloric acid or dilute sulfuric acid to give the nuclear chlorobenzamide probably through a

⁽²¹⁾ D. Ginsberg, J. Am. Chem. Soc., 73, 702 (1951).

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mechanism similar to that for the rearrangement of N-chloroanilides.

In the case of benzamide, the *ortho* and *para* positions are deactivated by electron withdrawal from the ring initiated by the carbonyl group, and since the hydrogen atom *meta* to the amido group is normally inactive, nuclear chlorination of benzamide does not occur. This is in accordance with the fact that direct chlorination of benzamide has not been reported.

The presence of "ortho-para directing" substituents in the nucleus of benzamide would increase the electron density of the ring, and provided that this activation was greater than the deactivating effect of the amido group, nuclear substitution would again be expected. Such strongly activating groups include hydroxy, amino and methoxy, and it was with these groups present in the nucleus of benzamide that nuclear chlorination was achieved. Weaker "ortho-para directing" groups, such as methyl and chloro, would not be expected to give any nuclear chlorination, and this was experimentally confirmed.

It is interesting to note that in some cases a relationship exists between the yield of N-chloroamide and the position and nature of the substituent(s) in the nucleus of the amide.

A study of the infrared curves of the N-chlorobenzamides shows the presence of (i) a secondary amide group, (ii) a carbonyl group, and (iii) two bands which are not given by their corresponding primary amides. It would appear that these two bands at 1272–1250 cm.⁻¹ (7.85–8.00 μ) and 910– 882 cm.⁻¹ (11.00–11.31 μ) are characteristic of the N–Cl linkage.

Experimental

Preparation of N-Chlorobenzamides.—The amide was dissolved in methanol and treated with an equimolecular quantity of *tert*-butyl hypochlorite and the reaction mixture allowed to stand in the dark for 12–20 hr. The product was poured into water, filtered, and dried in a desiccator over phosphorus pentoxide. With few exceptions the N-chloro compound was crystallized from benzene; Table Ia. A number of these compounds were also obtained by the action of sodium hypochlorite on the benzamide.

In the case of the chlorination of the 2- and 4-methoxybenzamides, when the reaction product was poured into water, the solid product which separated, in each case proved to be 5-chloro-2-methoxybenzamide, m.p. 137° (lit.,²³ m.p. 137-138°) and 3-chloro-4-methoxybenzamide m.p. 192-193° (lit. m.p. 193°²⁴) respectively; yield, 15%. The mother liquor in each case on further dilution with water gave the respective N-chloro derivatives; yield, 30%. However, when chlorination was carried out in the presence of 4% borax, only the N-chloro derivatives were obtained; Table Ib.

When boiled with 10% sodium hydroxide the N-chlorobenzamides were converted into the corresponding amines.

Rearrangement of N-Chloromethoxybenzamides.—N-Chloro-2-methoxybenzamide was dissolved in glacial acetic acid and 1 ml. of concentrated hydrochloric acid or dilute sulfuric acid added. The solution became yellow and was allowed to stand for 12 hr. The solution was then poured into water when 5-chloro-2-methoxybenzamide, m.p. 137°, was obtained.

N-Chloro-4-methoxybenzamide in a similar manner gave 3-chloro-4-methoxybenzamide, m.p. 192-193°.

Reaction between Salicylamide and tert-Butyl Hypochlorite.—A 13.7-g. sample (0.1 mole) of salicylamide was dissolved in methanol and 12 ml. of tert-butyl hypochlorite slowly added. It was necessary to cool the solution in icewater during the addition of the hypochlorite. After a few minutes white crystals separated from the solution. After 3 hr. the methanolic solution was poured into water and the white compound recrystallized from dilute alcohol, m.p. 226-227°. This compound gave no positive test for N-Cl with acidified potassium iodide.

The reaction was repeated under different temperature conditions and in the presence of borax or of sodium acetate. In each case the same chloro compound was obtained, m.p. 226-227°. This compound proved to be 2-hydroxy-5-chlorobenzamide (5-chlorosalicylamide) (lit.,²⁵ m.p. 226-227°); yield, 99%.

On hydrolysis with 30% sodium hydroxide 5-chloro-2hydroxybenzoic acid was obtained, m.p. 168° (lit.,²⁶ m.p. 167-168°).

Reaction between Anthranilamide and tert-Butyl Hypochlorite.—Anthranilamide was dissolved in glacial acetic acid and tert-butyl hypochlorite slowly added, with external cooling. A crystalline compound separated from the solution and proved to be 3,5-dichloroanthranilamide. M.p. $175-176^{\circ}$ (lit.,²⁷ m.p. 175-176°).

Hydrolysis of this compound gave 3,5-dichloroanthranilic acid, m.p. 232° (lit.,²⁸ m.p. 231-232°).

The Infrared Spectra.—All the infrared absorption curves were obtained from a Perkin–Elmer Infracord Model 137 spectrophotometer. Between 1.5 mg. and 2.0 mg. of Nchloroamide were compressed into pellets with 300 g. of potassium bromide at a pressure of 300 kg. per cm.⁻².

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