Rearrangement of Some Chlorosubstituted 3-Amino-3,4-dihydro-1-hydroxycarbostyrils in Hydrogen Halide Acids

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The general conditions and results of rearrangement studies of the 5-, 6-, 7-, and 8-chloro-substituted 3-amino-3,4-dihydro-1-hydroxycarbostyrils in concentrated hydrochloric and hydrobromic acids to the corresponding dihalosubstituted 3-amino-3,4-dihydrocarbostyrils have been described. The 5-, 7- and 8-chlorocarbostyrilhydroxamic acids undergo nucleophilic displacement by either chloride or bromide ion preferentially at the 6-position to form the respective 5,6-, 6,7- and 6,8-dihalolactams. However, with the 3-amino-6-chloro-3,4-dihydro-1-hydroxycarbostyril where the 6-position is blocked, nucleophilic displacement by halide ions occurs at the 8-position to afford the 6,8-dihalolactams. The 6,8-dichloro- and 6,8-dibromolactams were also prepared by alternative halogenation procedures for purposes of comparison with the rearrangement products.

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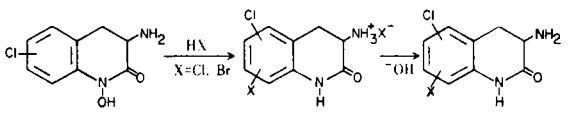
For some time now, 3-amino-3,4-dihydro-1-hydroxycarbostyril has been used in our laboratories as a model heterocyclic system for studying structure-activity relationships (1-5) and molecular rearrangements (6,7). In acidic media, this cyclic hydroxamic acid was found to rearrange to the corresponding 6-substituted lactams (7). Based on the conversion of the -NH(OH)CO- group as part of the heterocycle to the -NHCO- group and the displacement of the 6-benzenoid hydrogen by the nucleophile in the acidic medium, the rearrangement was described mechanistically as an acid-catalyzed, intermolecular heteroaromatic nucleophilic substitution (7). In a more recent study, the four isomeric chloro analogs of 3-amino-3,4-dihydro-1-hydroxycarbostyril were synthesized and examined for their antibacterial activities (5).

Because of our continued interest in the chemical and biological properties of 3-amino-3,4-dihydro-1-hydroxycarbostyril and related heterocyclic compounds, studies of the 5-, 6-, 7- and 8-chlorosubstituted derivatives I have now been extended to include their rearrangements in concentrated hydrochloric and hydrobromic acids to the corresponding dihalolactams III. The purpose of this paper is to describe the general conditions and results of these rearrangement studies.

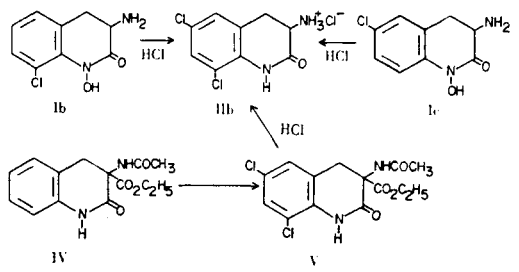


I II III

As summarized in Table I, the four chlorosubstituted 3-amino-3,4-dihydro-1-hydroxycarbostyrils were heated first in concentrated hydrochloric acid, and then in concentrated hydrobromic acid, under reflux conditions. The reaction times were based simply on the number of hours that were required for the reaction mixtures to give a negative hydroxamate test with ferric chloride reagent. The rearrangement products were first isolated from the reaction mixtures in the form of the quaternary ammonium halides II. The yields given in Table I were based on the halide salts II which were converted to the corresponding free bases III for elemental analysis. The melting points and microanalytical data of the products as the free bases III are recorded in Table II. These rearrangement products were found to be the dichloro (IIIa-IIIc) and the bromochloro (IIId-IIIg) substituted 3-amino-3,4-dihydrocarbostyrils from the concentrated hydrochloric acid and hydrobromic acid, respectively. The structural assignments of these dihalolactam products were based primarily on elemental and nmr spectral analyses. In addition, the structures of the two 6,8-dihalolactams were confirmed by alternate syntheses.

On refluxing in concentrated hydrochloric acid, the 7-chlorocarbostyrilhydroxamic acid Ia afforded a fairly good yield of the 6,7-dichlorolactam (IIIa). The structure of this product was readily deduced from its nmr spectrum

which indicated the presence of a broad singlet for the lactam proton at 0.4 τ and the absence of *ortho*- and *meta*-coupling in the aromatic signals (two proton singlets at 2.55 and 2.8 τ) and which verified that the entering chloro substituent occupied the 6 position. When the 8-chlorocarbostyrilhydroxamic acid (Ib) was treated similarly, the 6,8-dichlorolactam (IIIb) was produced in good yield. The nmr spectrum of this dichloro isomer showed a broad singlet (0.5 τ) for the lactam proton and a characteristic AB pattern (two doublets at 2.5 and 2.8 τ) with *meta*-coupling (J = 2 Hz) for the aromatic proton signals which are consistent with the 6,8-dichlorolactam structure.



Since both the 7-Cl and 8-Cl carbostyrilhydroxamic acids undergo nucleophilic substitution at only the 6 position, it follows that the reaction of 3-amino-6-chloro-3,4-dihydro-1-hydroxycarbostyril (Ic) in concentrated hydrochloric acid was of particular interest in this study because the 6 position already contains the chloro group. The product obtained from this reaction was identical in every respect (melting point, ir and nmr spectra) with the 6,8-dichlorolactam (IIIb) resulting from the rearrangement of the 3-amino-8-chloro-3,4-dihydro-1-hydroxycarbostyril (Ib) as described previously. Thus, heteroaromatic nucleophilic substitution occurs at position 8 of the carbostyril-hydroxamate system when the 6 position is blocked.

Besides the treatment of the 8-Cl and 6-Cl carbostyril-hydroxamic acids with concentrated hydrochloric acid to yield the same rearrangement product, the 6,8-dichlorolactam hydrochloride (IIb) was also obtained in fair yield by direct chlorination of 3-acetamido-3-carboethoxy-3,4-dihydrocarbostyril (IV) followed by hydrolysis of the dichloro intermediate V in concentrated hydrochloric acid as shown in the reaction scheme. The hydrolysis product had a melting point, ir and nmr spectra which were identical to those of the rearrangement products obtained from the two chlorocarbostyrilhydroxamic acids (Ib and Ic).

Treatment of the remaining 5-chlorocarbostyrilhydroxamic acid (Id) with concentrated hydrochloric acid under reflux conditions afforded yet another dichlorolactam as indicated by elemental analysis. The melting point, ir and nmr spectra of this product were different from those of the other two isomeric dichlorolactams. The nmr spectrum of the product showed the broad singlet at 0.5 τ for the lactam proton and an AB system for the

Table I

Results of the Rearrangement of Chlorosubstituted 3-Amino-3,4-dihydro-1-hydroxycarboxtyrils in Hydrogen Halide Acids

Reaction Substrate	Reaction Time	Dihalolactam Product	Yield %
	In Concentrated Hydrochloric Acid		
7-Cl (Ia)	4 hours	6,7-diCl (IIIa)	48
8-Cl (Ib)	5 hours	6,8-diCl (IIIb)	69
6-Cl (Ic)	5 hours	6,8-diCl (IIIb)	64
5-Cl (Id)	5 hours	5,6-diCl (IIIc)	79
	In Concentrated Hydrobromic Acid		
7-Cl (Ia)	5 hours	6-Br,7-Cl (IIId)	77
8-Cl (Ib)	4.5 hours	6-Br,8-Cl (IIIe)	72
6-Cl (Ic)	4 hours	8-Br,6-Cl (IIIf)	78
5-Cl (Id)	4 hours	6-Br,5-Cl (IIIg)	83

Table II

Melting Points and Analytical Data of the Dihalo-Substituted 3-Amino-3,4-dihydrocarbostyrils Prepared in This Study

Compound	Substituents	m.p. dec.	Composition	Carbon		Hydrogen		Nitrogen	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
IIIa	6,7-diCl	208-209°	$C_9H_8Cl_2N_2O$	46.78	47.06	3.49	3.22	12.12	11.86
IIIb	6,8-diCl	147-148°	$C_9H_8Cl_2N_2O$	46.78	46.80	3.49	3.19	12.12	11.97
IIIc	5,6-diCl	185-186°	$C_9H_8Cl_2N_2O$	46.78	46.58	3.49	3.52	12.12	11.97
IIId	6-Br, 7-Cl	175-180°	$C_9H_8BrClN_2$	39.23	39.43	2.93	2.92	10.17	10.40
IIIe	6-Br, 8-Cl	145-146°	$C_9H_8BrClN_2O$	39.23	39.37	2.93	3.13	10.17	9.96
IIIf	8-Br, 6-Cl	155-158°	$C_9H_8BrClN_2O$	39.23	39.10	2.93	2.94	10.17	10.08
IIIg	6-Br, 5-Cl	196-199°	$C_9H_8BrClN_2O$	39.23	38.90	2.93	3.01	10.17	9.93

aromatic proton signals which consisted of two doublets at 2.6 and 3.2 τ with an *ortho*-coupling constant (J = 9 Hz). From this data, coupled with the fact that only 6-substitution was observed with the 7-chloro and 8-chloro substrates as previously described, it was inferred that the chloro group was also located in the 6 position of the product. Consequently, the product was assigned the 5,6-dichlorolactam structure (IIIc).

When the experiments were repeated for the four chlorosubstituted 3-amino-3,4-dihydro-1-hydroxycarbostyrils (Ia-Id) in concentrated hydrobromic acid, the bromochlorolactams (IIId-IIIg) were produced even in higher yields than those of the dichlorolactams and were characterized by their melting points, ir and nmr spectra. As seen in Table I, the pattern of bromochlorolactams (IIId-IIIg) was identical to that of the dichlorolactam products (IIIa-IIIc). It should be noted that treatment of the 6-chloro and 8-chlorocarbostyrilhydroxamic acids with concentrated hydrobromic acid produced the 8-bromo-6-chloro (IIIf) and 6-bromo-8-chloro (IIIe) lactams, respectively. These results are in contrast to those observed when the same two heterocyclic compounds were treated with concentrated hydrochloric acid to yield the same reaction product, namely, 3-amino-6,8-dichloro-3,4-dihydrocarbostyril (IIIb). Similarly, with the 6-position blocked by the chloro group, the nucleophilic bromide ion attacks the 8-position to afford the 8-bromo-6-chlorolactam IIIf product. The latter product as the hydrobromide salt (IIf) was also obtained by independent synthesis from 3-amino-6-chloro-3,4-dihydrocarbostyril (7) by direct bromination.

From this study, the generality of the rearrangement of chlorocarbostyrilhydroxamic acids in hydrogen halide acids to the corresponding dihalolactams has been established. As was the case with the parent unsubstituted compound (7), the 5-, 7-, and 8-chloro substituted 3-amino-3,4-dihydro-1-hydroxycarbostyrils undergo nucleophilic displacement by halide ion strictly at the 6-position to form the respective 5,6-, 6,7-, and 6,8-dihalolactams. On the other hand, when the 6-position already contains the chloro substituent as in the 3-amino-6-chloro-3,4-dihydro-1-hydroxycarbostyril, nucleophilic substitution with the halide ions then occurs at the 8-position to yield the 6,8-dihalolactam products.

EXPERIMENTAL

General.

Melting points were determined on a Thomas-Hoover capillary melting apparatus and are uncorrected. Infrared spectra were recorded on a Beckman Model IR-10 spectrophotometer (potassium bromide) and were calibrated with polystyrene film. Nuclear magnetic resonance spectra were obtained with a Perkin-Elmer R-12B spectrometer at 60 MHz using trifluoroacetic acid as solvent and TMS as internal standard. The ir and nmr spectra of all the dihalolactams (IIIa-IIIg) were consistent with their proposed structures. Pertinent nmr data are presented in the discussion section. Microanalyses were performed by M-H-W Laboratories, Garden City, Michigan.

3-Aminochloro-3,4-dihydro-1-hydroxycarbostyrils (Ia-Id).

The 5-, 6-, 7- and 8-chlorosubstituted 3-amino-3,4-dihydro-1-hydroxycarbostyrils were synthesized according to previously described procedures and their physical properties agreed with those reported in the literature (5).

Rearrangement of the 3-Aminochloro-3,4-dihydro-1-hydroxycarbostyrils in Hydrogen Halide Acids.

The general procedure for this reaction was to heat a mixture of 200 mg. of the 3-aminochloro-3,4-dihydro-1-hydroxycarbostyril I in 20 ml. concentrated hydrochloric acid or hydrobromic acid under reflux conditions for the times indicated in Table I. In the case of the least soluble 3-amino-5-chloro-3,4-dihydro-1-hydroxycarbostyril (Id), 3 ml. of glacial acetic acid was added to the 20 ml. of concentrated hydrogen halide acids to effect solution. After cooling the reaction mixtures, the halide salts of the dihalolactams II which precipitated were recovered by filtration in yields given in Table I. For elemental analyses, the halide salts II were converted to the corresponding free bases III by dissolving them in water and adjusting the *p*H of the solution by addition of concentrated ammonium hydroxide or sodium hydroxide. See Table II for melting points and analytical data on the dihalolactam products (IIIa-IIIg).

3-Amino-6,8-dichloro-3,4-dihydrocarbostyril Hydrochloride (IIb).

This compound was prepared by an alternative method in which chlorine was introduced to a solution of 50 ml. of 50% aqueous ethanol containing 850 mg. of 3-acetamido-3-carboethoxy-3,4-dihydrocarbostyril (IV) (8) and 9.0 g. of potassium chloride at a moderate rate for 3 hours at 25°. The reaction mixture was chilled and the resulting precipitate was filtered, washed with water, and dried in a vacuum over phosphorus pentoxide to yield 370 mg. (35%) of 3-acetamido-3-carboethoxy-6,8-dichloro-3,4-dihydrocarbostyril (V), m.p. 238-240°. A 370 mg. sample of the latter compound was refluxed in 100 ml. of 6 *N* hydrochloric acid for 6 hours. The reaction mixture was chilled, and the resulting precipitate was filtered, washed with acetone, and dried in a vacuum over phosphorus pentoxide to yield 170 mg. (59%) of product as the hydrochloride salt. This compound was shown to be identical to the hydrochloride salt prepared by either the rearrangement of 3-amino-6-chloro-3,4-dihydro-1-hydroxycarbostyril (Ic) or 3-amino-8-chloro-3,4-dihydro-1-hydroxycarbostyril (Ib) in concentrated hydrochloric acid by a comparison of melting points and infrared spectra.

3-Amino-8-bromo-6-chloro-3,4-dihydrocarbostyril Hydrobromide (IIf).

An alternative procedure was used to prepare this compound. A 250 mg. sample of 3-amino-6-chloro-3,4-dihydrocarbostyril (5) was dissolved in 10 ml. of 70% aqueous methanol, and the solution was adjusted to *p*H 1.0 with 1 *N* hydrobromic acid. Bromine (0.94 g.) in 5 ml. of methanol was added dropwise to the above solution at 20°, and the reaction mixture was stirred for 48 hours. The latter was reduced to dryness *in vacuo*, and the resulting residue was washed with 20 ml. of acetone to yield 310 mg. (68%) of product as the hydrobromide salt. This compound was shown to be identical to the hydrobromide salt prepared by rearrangement of 3-amino-6-chloro-3,4-dihydro-1-hydroxycarbo-

styril (Ic) in concentrated hydrobromic acid by a comparison of melting points and infrared spectra.

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