A Comparative Study of the Rearrangement of Some 6- and 7-Halo-substituted 3-Amino-3,4-dihydro-1-hydroxycarbostyrils in Concentrated Hydrohalic Acids

Tommy J. McCord, Charles P. Crawford, James A. Rabon, Larry D. Gage, J. Mark Winter, and Alvie L. Davis

Department of Chemistry, Abilene Christian University, Abilene, Texas 79699

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The 6-bromo (**16**), 6-fluoro (**17**), 7-bromo (**14**), and 7-fluoro (**15**) substituted 3-amino-3,4-dihydro-1-hydroxycarbostyrils were treated with concentrated hydrochloric and hydrobromic acids under reflux conditions. The 7-halogenated *N*-hydroxycarbostyrils (**14,15**) gave the normal rearrangement products, the 6,7-dihalolactams (**18-21**). The 6-halogenated compounds (**16,17**) yielded the corresponding 6,8-dihalolactams (**22-24**) under the same experimental conditions, with the exception of the hydrobromic acid reaction of the 6-fluoro derivative **17** which yielded a mixture of products. Based on the comparison of the nmr spectrum of the product mixture with those of two authentic compounds, the mixture was identified as consisting of the normal rearrangement product, the 8-bromo-6-fluorolactam (**27**) and the straightforward reduction product, the 6-fluorolactam (**26**) in a ratio of about 2:1. The latter compounds were prepared by an independent method of synthesis in which 2-amino-5-fluorophenylalanine (**25**) was acidified to yield the corresponding lactam **26**, followed by bromination to afford the 8-bromo-6-fluorolactam **27**. A mechanism is proposed to interpret the experimental results of nucleophilic substitution with rearrangement and reduction which occur with the 6-fluoro compound **17** when exposed to bromide ions in strongly acidic solution.

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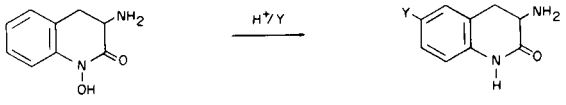
Previous studies (1,2) have shown the cyclic hydroxamic acid, 3-amino-3,4-dihydro-1-hydroxycarbostyril (**1**) undergoes rearrangement with weak nucleophiles (Y = H_2O, Cl^-, Br^-, CH_3OH) in acidic solution to yield the corresponding 6-substituted 3-amino-3,4-dihydrocarbostyrils



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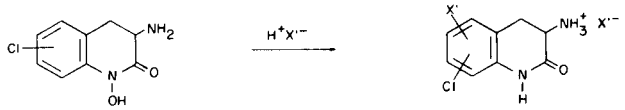
(**2**, Y = HO, Cl, Br, CH_3O). In a more recent study (3), the positional effects of the chloro substituent on the site of nucleophilic rearrangement was investigated by treatment of the 5-, 6-, 7- and 8-chlorinated 3-amino-3,4-dihydro-1-hydroxycarbostyrils (**3**) with concentrated hydrochloric



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and hydrobromic acids (X'^- = Cl^-, Br^-) under reflux conditions. Based on the various 5,6- 6,7- and 6,8-dihalo-substituted lactams (**4**, X′ = Cl, Br) thus obtained, the preferred site of nucleophilic substitution by chloride and bromide ions was the 6-position or the 8-position of **3** when the 6-position was blocked with the chloro group (3).

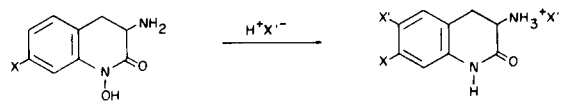
In order to compare further the effects of other halo substituents on the reaction of nucleophilic substitution with rearrangement when the 6-position is both unsubstituted and substituted, the 7-bromo (**14**), 7-fluoro (**15**), 6-bromo (**16**) and 6-fluoro (**17**) derivatives of **1** were synthesized and then treated with concentrated hydrochloric and hydrobromic acids under reflux conditions. We now wish to report the results of this comparative rearrangement study.

The results obtained from the treatment of the 7-bromo (**14**) and 7-fluoro (**15**) *N*-hydroxycarbostyrils in refluxing concentrated hydrochloric and hydrobromic acids for four hours are presented in Table I. In each case, substitution of the nucleophilic chloride and bromide ions (X'^- = Cl^-, Br^-) occurred preferentially at the 6-position to afford the corresponding 6,7-dihalolactams (**18-21**). In general, better yields of the 6,7-dihalolactams were obtained with concentrated hydrobromic acid than with hydrochloric acid. The structures of the 6,7-dihalolactams were confirmed by the nmr spectra, each of which showed a broad singlet for the lactam proton near δ 9.6. Whereas the 7-bromo-6-halolactams (**18,20**) show two singlets for the two aromatic protons (H_5 and H_8) in the δ 7.3-7.7 range, the 7-fluoro-6-halolactams (**19,21**) show a pair of doublets for the two aromatic protons (H_5 and H_8) in the δ 6.8-7.6 region. The additional splitting of the two aromatic protons of the latter compounds is attributed to the fluoro nuclei in the ring.

Table II summarizes the results of treating the 6-bromo (**16**) and the 6-fluoro (**17**) cyclic hydroxamates with concentrated hydrobromic and hydrochloric acids under reflux conditions for four hours. With the single exception of the 6-fluoro substrate (**17**) in hydrobromic acid, the 6-halo-substituted *N*-hydroxycarbostyrils **16, 17** in which the 6-position is blocked underwent nucleophilic substitution in the 8-position in the two concentrated hydrohalic acids to afford the corresponding 6,8-dihalolactams (**22-24**) in about the same yield. The nmr spectra of these products showed a broad singlet near δ 9.2-9.3 for the lactam pro-

Table I

Rearrangement of 7-Halosubstituted 3-Amino-3,4-dihydro-1-hydroxycarbostyrils in Concentrated Hydrohalic Acids



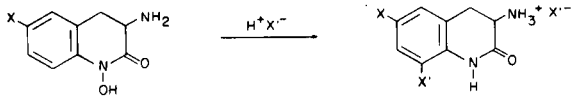
14, 15 18-21

Reaction Substrate	Substituent X	Nucleophile X'-	Dihalolactam Product	Substituents X', X	Yield % (a)
14	7-Br	Cl^-	**18**	6-Cl, 7-Br	70
15	7-F	Cl^-	**19**	6-Cl, 7-F	47
14	7-Br	Br^-	**20**	6-Br, 7-Br	80
15	7-F	Br^-	**21**	6-Br, 7-F	99

(a) Yields are based on hydrohalide salts.

Table II

Rearrangement of 6-Halosubstituted 3-Amino-3,4-dihydro-1-hydroxycarbostyrils in Concentrated Hydrohalic Acids



16, 17 22-24

Reaction Substrate	Substituent X	Nucleophile X'-	Dihalolactam Product	Substituents X', X	Yield % (a)
16	6-Br	Cl^-	**22**	6-Br, 8-Cl	55
17	6-F	Cl^-	**23**	6-F, 8-Cl	53
16	6-Br	Br^-	**24**	6-Br, 8-Br	54
17	6-F	Br^-	Mixture (b)		50 (c)

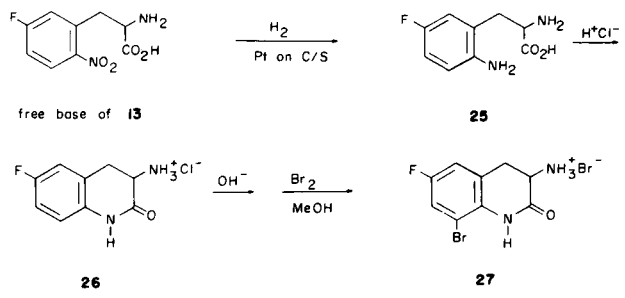
(a) Yields are based on hydrohalide salts. (b) A 2:1 mixture of 6-F, 8-Br (**27**) and 6-F, 8-H (**26**) lactams based on nmr and elemental analyses. (c) Yield is based on 2:1 mixture of products.

tons. The 6-bromo-8-halolactams (**22,24**) show a characteristic AB pattern (two doublets in the δ 6.9-7.5 range) with meta-coupling constants for the two aromatic protons, H_5 and H_7, which are consistent with the 6,8-dihalolactam structures (**22,24**). However, the 6-fluoro-8-chlorolactam (**23**) showed a less clearly observable AB pattern for the two aromatic protons because of broadening and overlapping of the signals in the δ 6.8-7.4 region. The infrared spectrum of **22** was identical to that of 3-amino-6-bromo-8-chloro-3,4-dihydrocarbostyril which was previously prepared by treatment of 3-amino-8-chloro-3,4-dihydro-1-hydroxycarbostyril with hydrobromic acid under reflux conditions (3).

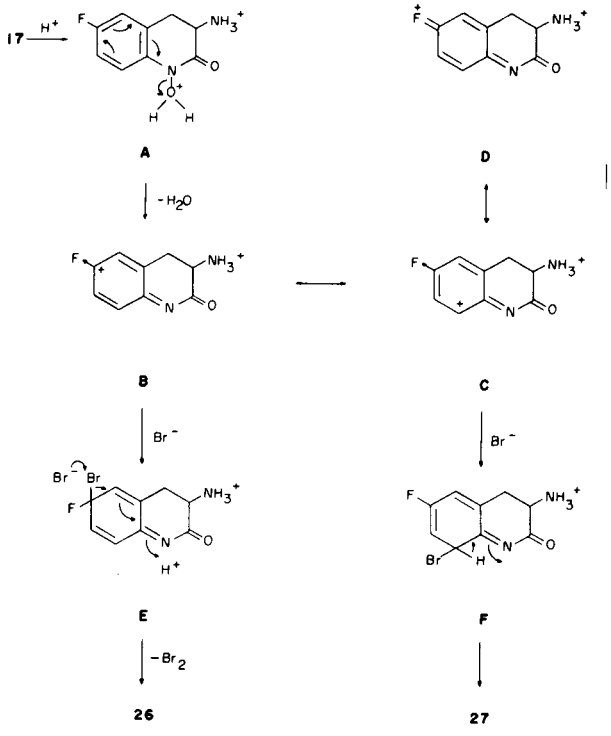
The most interesting result was obtained when the 6-fluoro reaction substrate (**17**) was treated with refluxing concentrated hydrobromic acid. The reaction mixture was observed to turn slightly red and was shown to contain bromine as indicated by a positive test with potassium iodide-starch indicator paper. In addition, the usual workup procedure of the reaction mixture yielded a solid consisting of two products. Several attempts to separate the reaction products by fractional crystallization methods were unsuccessful. Based on the nmr spectra of the product mixture in trifluoroacetic acid when compared with those of authentic compounds derived by independent synthesis, the mixture consisted of the normal rearrangement product, the 8-bromo-6-fluorolactam (**27**) and the reduction product, the 6-fluorolactam (**26**) in about a 2:1 ratio.

Authentic samples of the 3-amino-3,4-dihydro-6-fluorocarbostyril (**26**) and 3-amino-8-bromo-3,4-dihydro-6-fluorocarbostyril (**27**) were synthesized for comparative purposes as depicted in Scheme I. The hydrochloride salt of 5-fluoro-2-nitrophenylalanine (**13**) was first converted to the corresponding free base by neutralization with aqueous ammonia, and then hydrogenated in the presence of platinum on carbon (sulfided) to yield 2-amino-5-fluorophenylalanine (**25**). The latter compound was converted to

Scheme I



Scheme II



its corresponding lactam **26** by cyclization in acidic solution. In order to avoid mixed salt formation, the hydrobromide salt of **26** was prepared prior to bromination with a solution of excess bromine in methanol to afford the desired 8-bromo-6-fluorolactam hydrobromide (**27**). The nmr spectra of **26** and **27** in trifluoroacetic acid showed a chemical shift difference of δ 9.25 and δ 9.6, respectively, for the lactam protons which were used as the criteria for determining the relative amounts of the same two products in the mixture obtained from the treatment of the 6-fluoro hydroxamate (**17**) with concentrated hydrobromic acid.

Since the 6-fluoro *N*-hyroxycarbostyril **17** was the only substrate observed to undergo both reduction and nucleophilic substitution in concentrated hydrobromic acid, the ability of the bromide ion to act as a reducing agent as well as a nucleophile was dependent upon the nature and position of the halo substituent in the carbostyril ring. Therefore, in the presence of bromide ion it appears that the 6-fluoro substituent of **17** facilitates the reduction to the 6-fluoro lactam **26** in a manner which is not observed for the corresponding 6-bromo hydroxamate **16**.

Speculative interpretation of this substituent effect is presented in Scheme II which accounts for the formation of both the reductive and rearranged products. In accord with our previously suggested mechanism (2), protonation of the 1-hydroxy oxygen of **17** occurs with formation of the conjugate acid **A** which undergoes heterolytic cleavage of the N-O bond with loss of water and accompanying resonance interaction with the aromatic π system to form two iminocyclohexadienyl cations (**B** and **C**) with distribution of the positive charge to the 6- and 8-positions.The fluoro group in the 6-position exerts an electron-withdrawing inductive effect (-I) to destabilize the two cyclohexadienyl cations. This inductive effect is stronger at the 6-position (**B**) to which fluorine is bonded than at the 8-position (**C**). On the other hand, the fluorine is able to conjugate its unshared electrons with the electron-deficient ring, and thus exerts a resonance effect (+R) which stabilizes the intermediates (**B** and **C**) by further delocalization of the positive charge by formation of the fluoronium ion **D**. Most likely, then, these two opposing effects approximately cancel for the 6-fluoro substituent and the net result is that both the 6- and 8-positions are activated sufficiently for nucleophilic attack, but not to the same degree.

Even though the fluoro substituent is already situated on the preferred 6-position for nucleophilic substitution, this position is not blocked as in the case of the 6-chloro (3) and 6-bromo substituents. The fluorine is a much smaller atom than the chlorine and bromine atoms, and thus provides a less hindered approach (steric effect) for the nucleophile to attack the 6-position to which it is bonded. However, unlike the 8-position which is susceptible to attack by both the nucleophilic chloride and bromide ions, the less activated 6-position is susceptible to attack only by the more concentrated and stronger nucleophilic bromide ion. Thus, each of the two cyclohexadenium ions (**B** and **C**) react with the nucleophilic bromide ion to afford the corresponding dihalocyclohexadienimino intermediates (**E** and **F**).

The driving force of both dihalo intermediates **E** and **F** is the restoration of the π-electron system of the benzene ring. The 8-bromo-6-fluoro intermediate **F** simply undergoes proton transfer to yield the more stable tautomeric 8-bromo-6-fluorolactam **27**. However, the 6-bromo-6-fluoro intermediate **E** cannot undergo a similar prototropic change. Instead, it undergoes reduction by elimination of the bromenium ion (Br^+) facilitated by the bromide ion to

effect rearomatization of the ring and protonation of the hetero nitrogen atom with formation of the 6-fluorolactam (**26**) and bromine.

A peculiarity of the Bamberger rearrangements (4-6) of halosubstituted phenylhydroxylamines in concentrated hydrochloric or hydrobromic acid was the formation of aniline with loss of halogen whereupon halogen was available for polyhalogenation of aniline to form dihaloanilines. In a separate experiment, the 6-fluorolactam (**26**) was treated with an equimolar amount of bromine in a proportionate volume of concentrated hydrobromic acid under reflux conditions for four hours. Since practically all of the starting material **26** was recovered, it was concluded that none of the 8-bromo-6-fluorolactam (**27**) arises from the *in situ* electrophilic bromination of the reduced product, the 6-fluorolactam (**26**). Therefore, the major product **27** results from an acid-catalyzed nucleophilic substitution of **17** by bromide ion as previously described.

In summary, a mechanism has been suggested which provides an interpretation that is consistent with the experimental results for the nucleophilic substitution with rearrangement and reduction of 3-amino-3,4-dihydro-6-fluoro-1-hydroxycarbostyril when treated with concentrated hydrobromic acid. In addition, this study shows the influence of the nature and position of halo substituents on the acid-catalyzed nucleophilic substitution of 3-amino-3,4-dihydro-1-hydroxycarbostyrils in concentrated hydrohalic acids.

EXPERIMENTAL

General.

Melting points were determined on a Thomas-Hoover capillary melting point 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 deuterium oxide-deuterium chloride as solvent and sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as the internal standard, and trifluoroacetic acid as the solvent and tetramethylsilane (TMS) as the internal standard. The ir and nmr spectra of all the carbostyrilhydroxamic acids (**14-17**) and dihalolactams (**18-24, 27**) were consistent with their proposed structures. Pertinent nmr data are presented in the discussion section. Microanalyses were performed by M-H-W Laboratories, Phoenix, Arizona.

Halo-2-nitrobenzyl Bromides (**5-7**).

These compounds were prepared from the corresponding halo-2-nitrotoluenes in a manner similar to that described for the synthesis of 5-bromo-2-nitrobenzyl bromide (2). The analytical sample of the 4-F compound (**6**) was a liquid obtained by vacuum distillation techniques. However, vacuum distillation (127°, 9 mm) of the 5-F derivative (**7**) followed by the addition of heptane to the distillate and chilling at −17° gave a crystalline product. The latter was recrystallized from 95% aqueous ethanol. The bp, mp, yields and analytical data are given in Table III.

Ethyl 2-Acetamido-2-(halo-2′-nitrobenzyl)malonates (**8-10**).

These compounds were synthesized from the condensation of the halo-2-nitrobenzyl bromides (**5-7**) with ethyl acetamidomalonate in accord with the procedure previously described for the synthesis of ethyl 2-acetamido-2-(5′-bromo-2′-nitrobenzyl)malonate (2). Melting points, yields, and analyses are given in Table III.

Table III

Physical Constants, Yields, and Analytical Data of Some Halosubstituted 3-Amino-3,4-dihydro-1-hydroxycarbostyrils and the Corresponding Intermediates Prepared in This Study

Compound	Substituents	Mp, °C	Yield, %	Composition	Carbon		Hydrogen		Nitrogen	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
				Halo-2-nitrobenzyl Bromides						
5	4-Br	48-52	68	$C_7H_5Br_2NO_2$	28.52	28.39	1.71	1.92	4.75	4.59
6	4-F	81-82(6mm)(a)	45	$C_7H_5BrFNO_2$	35.92	35.68	2.15	2.07	5.99	5.79
7	5-F	43-44	35	$C_7H_5BrFNO_2$	35.92	35.73	2.15	1.98	5.99	5.70
				Ethyl 2-Acetamido-(halo-2′-nitrobenzyl)malonates						
8	4-Br	134-135	68	$C_{16}H_{19}BrN_2O_7$	44.56	44.48	4.44	4.36	6.50	6.40
9	4-F	115-116	53	$C_{16}H_{19}FN_2O_7$	51.89	51.71	5.17	5.19	7.57	7.33
10	5-F	126-128	53	$C_{16}H_{19}FN_2O_7$	51.89	51.65	5.17	5.29	7.57	7.53
				Halo-2-nitrophenylalanines						
11	4-Br	210-216	90	$C_9H_9BrN_2O_4 \cdot HCl$	33.20	33.06	3.10	3.20	8.61	8.67
12	4-F	212-213	62	$C_9H_9FN_2O_4 \cdot HCl$	40.84	40.66	3.81	3.76	10.59	10.79
13	5-F	222-230	87	$C_9H_9FN_2O_4 \cdot HCl$	40.84	40.73	3.81	3.84	10.59	10.53
				3-Amino-3,4-dihydro-halo-1-hydroxycarbostyrils						
14	7-Br	260-263	82	$C_9H_9BrN_2O_2 \cdot HCl$	36.82	36.67	3.43	3.54	9.55	9.32
15	7-F	263-264	89	$C_9H_9FN_2O_2 \cdot HCl$	46.46	46.43	4.33	4.27	12.04	12.10
16	6-Br	262-264	89	$C_9H_9FN_2O_2 \cdot HCl$	36.82	37.01	3.43	3.62	9.55	9.55
17	6-F	259-261	76	$C_9H_9FN_2O \cdot HCl$	46.46	46.36	4.33	4.14	12.04	12.12

(a) Boiling point.

Table IV

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

Compound	Substituents	Mp dec	Composition	Carbon		Hydrogen		Nitrogen	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
18	6-Cl, 7-Br	328-333°	$C_9H_8BrClN_2O \cdot HCl$	34.64	34.88	2.91	2.94	8.98	8.99
19	6-Cl, 7-F	312-315°	$C_9H_8ClFN_2O \cdot HCl$	43.05	43.08	3.61	3.74	11.16	11.23
20	6,7 diBr	347-348°	$C_9H_8Br_2N_2O \cdot HBr$	26.96	27.17	2.26	2.41	6.99	7.04
21	6-Br, 7-F	335-340°	$C_9H_8BrFN_2O \cdot HBr$	31.79	32.00	2.67	2.75	8.24	8.11
22	6-Br, 8-Cl (a)	320-325°	$C_9H_8BrClN_2O \cdot HCl$	34.64	34.49	2.91	3.13	8.98	8.73
23	8-Cl, 6-F	280-290°	$C_9H_8ClFN_2O \cdot HCl$	43.05	42.96	3.61	3.85	11.16	10.96
24	6,8 diBr (b)	155-156°	$C_9H_2Br_2N_2O$	33.78	33.59	2.52	2.24	8.75	8.59

(a) Analyzed previously (3) as the free base. (b) Analyzed as the free base.

Halo-2-nitrophenylalanine Hydrochlorides (**11-13**).

The same acid hydrolysis procedure was followed for the preparation of these compounds from the corresponding malonate derivatives (**8-10**) as previously reported for 5-bromo-2-nitrophenylalanine hydrochloride (2). The mp, yields, and analyses of these compounds are given in Table III.

3-Amino-3,4-dihydro-halo-1-hydroxycarbostyrils (**14-17**).

These compounds were obtained by reductive cyclization of corresponding halo-2-nitrophenylalanine hydrochlorides in a manner similar to that previously reported for the preparation of the 6- and 7-chloro derivatives of 3-amino-3,4-dihydro-1-hydroxycarbostyril hydrochloride (7). These compounds gave the characteristic color reaction (violet) with ferric chloride reagent. Melting points, yields, and analyses are given in Table III.

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

The general procedure involved heating a 200 mg sample of the halogenated 3-amino-3,4-dihydro-1-hydroxycarbostyril (**14-17**) in 20 ml of concentrated hydrochloric or hydrobromic acid under reflux conditions for 4 hours as indicated in Tables I and II. To avoid the formation of mixed hydrohalide salts during rearrangement, ammonium hydroxide was added to an aqueous solution of 200 mg of the hydrochloride salt to precipitate the free base which was recovered by filtration, and then introduced to the 20 ml of concentrated hydrobromic acid. The hot solutions were then treated with activated carbon which was removed by filtration through celite. In cases of the more soluble dihalolactams it was necessary to reduce the volume of the solutions *in vacuo* to almost dryness. The precipitates which formed on cooling were removed by filtration on sintered-glass crucibles, washed with acetone, dried *in vacuo* over phoshorus pentoxide to give the corresponding dihalolactams (**18-24**) as given in Table IV. In most cases the halide salts of the dihalolactams were analyzed. The free base of **24** was formed by dissolving the halide salt in water and adjusting the *p*H of the solution by addition of ammonium hydroxide. Table IV gives the melting points and analytical data on the dihalolactam products (**18-24**).

2-Amino-5-fluorophenylalanine (**25**).

A 200 mg sample (0.88 mmole) of 5-fluoro-2-nitrophenylalanine, 238-240° mp prepared by treatment of its hydrochloride salt with ammonium hydroxide to *p*H 7, was dissolved in 15 ml of water and hydrogenated in the presence of 20 mg of Pt/C (sulfided) catalyst at 3.67 kg/cm² of hydrogen pressure for 18 hours. The volume of the solution was reduced *in vacuo* to dryness and the residue was washed with acetone to give 130 mg (75%) of product, 178-180°.

Anal. Calcd. for $C_9H_{11}FN_2O_2$: C, 54.54; H, 5.60; N, 14.14. Found: C, 54.73; H, 5.49; N, 14.24.

3-Amino-3,4-dihydro-6-fluorocarbostyril Hydrochloride (**26**).

To a 100 mg sample (0.51 mmole) of 2-amino-5-fluorophenylalanine, dissolved in 10 ml of water, was added 10 ml of concentrated hydrochloric acid. The solution was chilled overnight to yield 80 mg (73%) of product, mp 325-332°.

Anal. Calcd. for $C_9H_9FN_2O \cdot HCl$: C, 49.89; H, 4.65; N, 12.93. Found: C, 50.00; H, 4.71; N, 12.73.

3-Amino-8-bromo-3,4-dihydro-6-fluorocarbostyril Hydrobromide (**27**).

To a 500 mg sample (1.8 mmoles) of 3-amino-3,4-dihydro-6-fluorocarbostyril hydrobromide, prepared by treatment of the free base of **26** with hydrobromic acid dissolved in 20 ml of 70% aqueous methanol, was added a solution of 1.84 g of bromine (11.5 mmoles) and 5 ml of 70% aqueous methanol. The resulting solution was stirred in a stoppered flask for 72 hours at 25°, treated with activated charcoal and filtered through celite. The volume of the filtrate was reduced *in vacuo*, and the resulting precipitate was washed with ether to give 0.44 g (68%) of product, mp 286-288°.

Anal. Calcd. for $C_9H_8BrFN_2O \cdot HBr$: C, 31.79; H, 2.67; N, 8.24. Found: C, 31.73; H, 2.89; N, 8.14.

In a separate experiment, a solution of 200 mg (0.76 mmole) of the hydrobromide salt of **26** and 122 mg (0.76 mmole) of bromine in 20 ml of concentrated hydrobromic acid was heated under reflux for four hours. Nearly a quantitative amount (180 mg) of unreacted starting material was recovered from the reaction mixture. The ir spectrum of the compound was identical to that of the hydrobromide salt of **26**.

Reaction of 3-Amino-3,4-dihydro-6-fluoro-1-hydroxycarbostyril (**17**) with Concentrated Hydrobromic Acid.

A solution of 150 mg (0.77 mmole) of the free base of **17** in 15 ml of concentrated hydrobromic acid was heated under reflux for four hours. After the first hour of heating, the reaction mixture was red and the droplets of condensate which collected on the inner drip tip of the condenser were also red. The vapor which escaped from the top of the condenser gave a positive test (blue) with iodide-starch indicator paper. The latter test and the characteristic coloration of the reaction mixture indicated the formation of free bromine in the presence of bromide ion. At the end of the reflux period, the reaction mixture failed to give a positive ferric hydroxamate test (violet). The hot dark reaction mixture was treated with activated charcoal and then passed through a filter pad of Celite. The filtrate was taken to dryness *in vacuo* by removal of the hydrobromic acid and the residue was dissolved in a minimum amount of boiling 50% aqueous ethanol. After chilling the solution at −17° overnight, the solid which formed was collected on a filter, washed with acetone, and dried *in vacuo* over phosphorus pentoxide. The solid (100

mg) gave an mp 300-305°; C, 35.44; H, 3.19; and N, 9.11; nmr (CF_3CO_2H) δ 3.4-3.9 (d, 2, J = 10 Hz, CH_2), 4.3-5.0 (br m, 1, CH), 6.9-7.5 (m, 3-2, Ar-H), 9.25 and 9.6 (br s, 1, NH). It was shown by both elemental and spectral analysis to be a 2:1 mixture of the 8-bromo-6-fluorolactam **27** and the 6-fluorolactam **26**, respectively. Further attempts to separate the product mixture by fractional crystallization methods and by column chromatography using alumina were unsuccessful.

Acknowledgment.

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