The Rearrangement of 3-Amino-3,4-dihydro-1-hydroxycarbostyril in Acidic Media (1)

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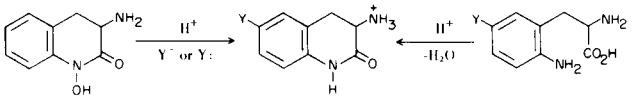
Recently, we reported that 3-amino-3,4-dihydro-1-hydroxycarbostyril (I) rearranges to 3-amino-3,4-dihydro-6-hydroxycarbostyril (II, Y = OH) in dilute aqueous sulfuric acid under reflux conditions (3). As an extension of this investigation, we now wish to describe our studies



I II III

on the rearrangement of the same heterocyclic system (I) in other acidic media. The rearrangement media and conditions employed for these studies are presented in Table I together with the corresponding products (II) and their yields.

In a manner strictly analogous to that observed previously (3), I rearranges in acidic solution to yield the corresponding 6-substituted lactam (II), 3-amino-3,4-dihydrocarbostyril, according to reaction conditions. The reaction of I in concentrated hydrobromic acid gave the 6-bromo rearrangement product (II, Y = Br) in good yield. With concentrated hydrochloric acid, the 6-chloro (Y = Cl) derivative of II was formed in excellent yield, whereas with dilute aqueous hydrochloric acid, a good yield of the 6-hydroxy lactam (II, Y = OH) was obtained. In order to effect the rearrangement of I in dilute methanolic sulfuric acid, the best conditions found were heating in a bomb tube at 125° for 22 hours, which afforded a good yield of the 6-methoxy (Y = OCH_3) derivative of II. Initial attempts to carry out the latter transformation by prolonged heating under reflux conditions only gave the starting material.

The various 3-amino-3,4-dihydro-6-(substituted)carbostyrils from the rearrangement of I were isolated in the form of either their hydrochloride salts or free bases, and were unequivocally identified by melting points, R_f values, and infrared spectral analyses with authentic specimens *via* cyclization of the corresponding 2-amino-5-(substituted)phenylalanines (III) through lactam formation in acidic solution. The physical constants, yields, and analytical data of the 6-substituted derivatives of 3-amino-3,4-dihydrocarbostyril are given in Table II.

The requisite 2-amino-5-(substituted)phenylalanines (III) for lactam formation were prepared by catalytic hydrogenation of the corresponding free bases of 5-(substituted)-2-nitrophenylalanines under neutral conditions. In order to prevent the hydrogenolysis of the 5-bromo and 5-chloro substituents, a special hydrogenation

TABLE I

Data on Rearrangement Studies of 3-Amino-3,4-dihydro-1-hydroxycarbostyril

Rearrangement Media and Conditions	Nucleophile Y^- or Y:	Rearrangement Product (II)	Yield %
Concentrated hydrobromic acid under reflux for 5 hours	Br^-	3-Amino-6-bromo-3,4-dihydrocarbostyril	66
Concentrated hydrochloric acid under reflux for 5 hours	Cl^-	3-Amino-6-chloro-3,4-dihydrocarbostyril	90
1 *N* hydrochloric acid under reflux for 5 hours	H_2O	3-Amino-3,4-dihydro-6-hydroxycarbostyril	60
Methanolic sulfuric acid (a) at 125° for 22 hours	CH_3OH	3-Amino-3,4-dihydro-6-methoxycarbostyril	75

(a) 10 ml. of absolute methanol:4 drops of concentrated sulfuric acid.

TABLE II

Physical Constants, Yields, and Analytical Data of 3-Amino-3,4-dihydro-6-(substituted)carbostyrils (II) (a)

6-Substituent	M.p. (b) (dec.)	R_f (c)	Yield %	Composition	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
-Br	324-325°	0.64 (A), 0.78 (B)	46	$C_9H_9N_2OBr \cdot HCl$	39.94	39.54	3.63	3.64	10.09	9.86
-Cl	171-172°	0.67 (A), 0.77 (B)	78	$C_9H_9N_2OCl$	54.98	55.02	4.61	4.59	14.25	14.34
$-OCH_3$	302-303°	0.50 (A), 0.87 (B)	83	$C_{10}H_{12}N_2O_2 \cdot HCl$	52.52	52.56	5.73	5.77	12.25	12.25

(a) *Via* cyclization of 2-amino-5-(substituted)phenylalanines. (b) Melting points (dec.) are for analytical samples. (c) The R_f values given for the appropriate solvents given by letter: A, 1-butanol-acetic acid-water (3:1:1); B, 65% pyridine.

TABLE III

Physical Constants, Yields, and Analytical Data of 2-Amino-5-(substituted)phenylalanines (III)

5-Substituent	M.p. (b)	R_f (c)	Yield %	Composition	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
-Br	195-197°	0.64 (A), 0.62 (B)	70	$C_9H_{11}N_2O_2Br$	41.72	41.87	4.28	4.21	10.81	10.55
-Cl	183-184°	0.72 (A), 0.67 (B)	85	$C_9H_{11}N_2O_2Cl$	50.36	50.33	5.17	5.06	13.05	12.80
$-OCH_3$	156-157°	0.55 (A), 0.66 (B)	76	$C_{10}H_{14}N_2O_3$	57.13	56.93	6.71	6.58	13.33	13.28

(b,c) Same footnote notations as given in Table II.

TABLE IV

Physical Constants, Yields, and Analytical Data of 5-(Substituted)-2-nitrophenylalanines

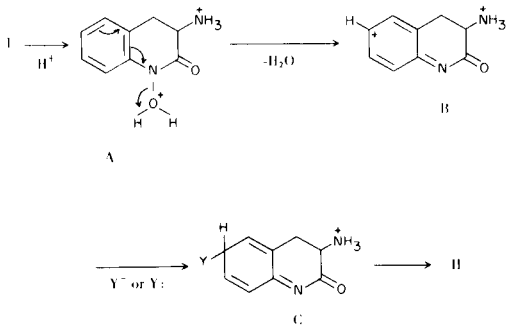
5-Substituent	M.p. (b)	R_f (c)	Yield %	Composition	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
-Br	237-243°	0.59 (A), 0.68 (B)	66	$C_9H_9N_2O_4Br$	37.39	37.62	3.14	3.21	9.64	9.62
-Cl	225-226°	0.66 (A), 0.69 (B)	80	$C_9H_9N_2O_4Cl \cdot HCl$	38.46	38.38	3.59	3.53	9.97	9.73
$-OCH_3$	230-231°	0.52 (A), 0.78 (B)	83	$C_{10}H_{12}N_2O_5 \cdot HCl$	43.41	43.31	4.74	4.71	---	---

(b,c) Same footnote notations as given in Table II.

catalyst (4) was employed for the reduction of the 5-halo-2-nitrophenylalanines to the 2-amino-5-halophenylalanines. Yields, physical characteristics and analytical data of the 2-amino-5-(substituted)phenylalanines (III) are compiled in Table III.

The 5-(substituted)-2-nitrophenylalanines were obtained *via* an ethyl acetamidomalonic ester synthesis using the appropriately 5-substituted-2-nitrobenzyl bromides for the condensation reactions as described in the Experimental section. These compounds are listed in Table IV with their yields, physical constants, and analytical data.

In general, several common features were observed in each instance of the molecular rearrangement of I. Under the influence of acidic conditions, the reaction of I led to lactam (-NHCO-) formation with loss of its original hydroxamate function [-N(OH)CO-], which was followed by a gradual change of its characteristic violet color with ferric chloride reagent. The transformation occurs smoothly affording a reaction mixture from which only a single rearrangement product was obtained, which indicates the substitution takes place preferentially on the 6-position of the dihydrocarbostyril ring. The identity of the substituent (Br, Cl, OH or OCH_3) at the 6-position of II depends on the presence of the nucleophile (Br^-, Cl^-, H_2O, CH_3OH) in the acidic medium. These results clearly indicate that the 6-substituted derivatives of II arise from a straightforward acid-catalyzed intermolecular rearrangement of I *via* nucleophilic heteroaromatic substitution, and suggest the following mechanism:



Protonation of I to A, followed by heterolysis of the N-O bond with loss of a water molecule, gives preferentially the mesomeric intermediate carbonium ion B. The combination of B with the nucleophilic anion (Y^-) or molecule (Y:) forms C, which undergoes a prototropic change to the product II. The stages of this mechanism are similar to those first proposed by Heller, Hughes and Ingold (5) to explain the formation of Bamberger's products from arylhydroxyamines.

3-Amino-3,4-dihydro-1-hydroxycarbostyril constitutes a heterocyclic system which is ideally suited for rearrangement studies in acidic solvent media. By virtue of the $-NH_2$ group, both starting material and rearrangement products are soluble in various acidic reaction media and give color reactions with ninhydrin reagent, which enables qualitative analysis by paper chromatography of the reaction mixture. The presence of its -N(OH)CO- group is detected discriminately by simple characterization tests (*i.e.*, ferric chloride and Fehlings), which serve to determine the reaction times for completion of the rearrangements under the experimental conditions. The -NHCO- group as part of the heterocycle of the rearrangement products is markedly stable to further transformations, particularly under strong acid conditions. Also, the structures of the products of rearrangement can be established by direct synthesis *via* lactam formation of the corresponding ring-substituted derivatives of *o*-aminophenylalanine.

In the context of this work, we have described a proton-catalyzed rearrangement characteristic of a heterocyclic hydroxamic acid, 3-amino-3,4-dihydro-1-hydroxycarbostyril, in which further rearrangement studies with the 6-position blocked are forthcoming.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. The infrared analyses were performed on a Beckman IR-10 spectrophotometer using the potassium bromide technique. The R_f data were determined using the ascending technique in the solvents indicated, and ninhydrin reagent was used for development of the spots. The microanalyses were performed by M-H-W Laboratories, Garden City, Michigan.

3-Amino-3,4-dihydro-6-(substituted)carbostyrils.

Via Rearrangement of 3-Amino-3,4-dihydro-1-hydroxycarbostyril.

In Concentrated Hydrobromic Acid Under Reflux.

Under conditions described in Table I, a 100 mg. sample of 3-amino-3,4-dihydro-1-hydroxycarbostyril was treated with 25 ml. of this acid. Subsequent reduction in volume and cooling resulted in the formation of 120 mg. of the hydrobromide of 3-amino-6-bromo-3,4-dihydrocarbostyril, m.p. 319-320° dec. The latter compound was converted to its free base by precipitating from aqueous solution with ammonium hydroxide, and then subsequent treatment of the free base with hydrochloric acid formed the corresponding hydrochloride salt.

In Concentrated Hydrochloric Acid Under Reflux.

In a similar manner as described above, 25 ml. of this media was used to convert 100 mg. of 3-amino-3,4-dihydro-1-hydroxycarbostyril to 100 mg. of 3-amino-6-chloro-3,4-dihydrocarbostyril hydrochloride, m.p. 322-323°.

In 1*N* Hydrochloric Acid Under Reflux.

A 250 mg. sample of 3-amino-3,4-dihydro-1-hydroxycarbostyril was treated with 25 ml. of this media as described in Table I. Successive reductions in volume of the solution *in vacuo* and precipitations gave a total of 195 mg. of 3-amino-3,4-dihydro-6-hydroxycarbostyril hydrochloride, previously prepared *via* a different route (3).

In Methanol/H^+ at 125°.

As described in Table I a mixture of 10 ml. of methanol, 4 drops of concentrated sufluric acid and 250 mg. of 3-amino-3,4-dihydro-1-hydroxycarbostyril was kept in a stainless steel reaction bomb. The solution was then diluted with a few ml. of water, neutralized with sodium hydroxide and reduced to dryness *in vacuo*. The residue was dissolved in a small amount of methanol and the solution was dried over anhydrous sodium sulfate. After filtration the solution was acidified with anhydrous hydrogen chloride. Chilling of the solution and treatment with ethyl ether gave a total of 240 mg. of 3-amino-3,4-dihydro-6-methoxycarbostyril hydrochloride. This product was recrystallized from methanol-ethyl ether.

In each case, the physical properties (see Table II) and infrared spectra of the products of rearrangement were identical to those recorded for the authentic compounds, which are subsequently described below.

Via Cyclization of 2-Amino-5-(substituted)phenylalanines.

3-Amino-6-bromo-3,4-dihydrocarbostyril Hydrochloride.

To a 100 mg. sample of 2-amino-5-bromophenylalanine dissolved in 25 ml. of 50% aqueous methanol was added 25 ml. of concentrated hydrochloric acid. The volume of the solution was reduced *in vacuo* to about 5 ml. After chilling overnight the precipitate was filtered, washed with acetone, and dried over phosphorus pentoxide to give 50 mg. of product (see Table II). The infrared spectrum of 3-amino-6-bromo-3,4-dihydrocarbostyril hydrochloride showed major absorption bands at 3.1, 3.5 (broad), 5.9 (broad), 6.3, 6.7, 7.0, 7.15, 7.35, 7.6, 8.3, 9.25, 10.9, 11.9 and 12.0 μ.

3-Amino-6-chloro-3,4-dihydrocarbostyril.

In a similar manner as described above a 100 mg. sample of 2-amino-5-chlorophenylalanine was converted to 85 mg. of the hydrochloride of 3-amino-6-chloro-3,4-dihydrocarbostyril. The infrared spectrum of the latter compound showed major absorp-

tion bands at 3.15, 3.2, 3.45 (broad), 3.7, 5.95, 6.4, 6.75, 7.4, 7.6, 7.7, 8.1, 8.4, 8.7, 12.25 and 13.0 μ. Conversion to the free base product was accomplished by treatment of the latter with ammonium hydroxide to *p*H 7 (see Table II).

3-Amino-3,4-dihydro-6-methoxycarbostyril Hydrochloride.

A 1.0 g. sample of 5-methoxy-2-nitrophenylalanine, m.p. 224-225°, prepared by treatment of the hydrochloride with ammonium hydroxide, was dissolved in 30 ml. of 50% aqueous methanol and reduced at 3.67 kg./cm^2 of hydrogen pressure in the presence of 50 mg. of platinum black for 3 hours. After removal of the catalyst by filtration, 30 ml. of concentrated hydrochloric acid and 5 ml. of acetone were added to the filtrate. The resulting precipitate was filtered and recrystallized from methanol-hydrochloric acid to yield 0.8 g. of product (see Table II). The infrared spectrum showed major absorption bands at 3.45 (broad), 5.85, 6.25, 6.3, 6.7, 6.9, 7.1, 7.8, 7.9, 8.0, 8.6, 9.0, 9.7, and 12.1 μ.

2-Amino-5-(substituted)phenylalanines.

2-Amino-5-bromophenylalanine.

A 400 mg. sample of 5-bromo-2-nitrophenylalanine suspended in 10 ml. of 50% aqueous methanol was reduced at 3.67 kg./cm^2 hydrogen pressure for 10 hours in the presence of 80 mg. of platinum on carbon, sulfided (purchased from Engelhard Industries). The catalyst was removed by filtration, and the volume of the filtrate was reduced *in vacuo* to about 5 ml. After cooling, the resulting precipitate was filtered and recrystallized from hot ethanol to yield 250 mg. of product (see Table III).

2-Amino-5-chlorophenylalanine.

In a similar manner as described above a 1.0 g. sample of 5-chloro-2-nitrophenylalanine, m.p. 232-233°, prepared from the hydrochloride by treatment with ammonium hydroxide, was converted to 740 mg. of product (see Table III).

2-Amino-5-methoxyphenylalanine.

This compound was prepared in a similar manner as described above with the exception that platinum black was used as the catalyst. A 1.0 g. sample of 5-methoxy-2-nitrophenylalanine, m.p. 224-225°, prepared from the hydrochloride by treatment with ammonium hydroxide, was converted to 630 mg. of product (see Table III).

5-(Substituted)-2-nitrophenylalanines.

5-Bromo-2-nitrophenylalanine.

A 10.0 g. sample of ethyl 2-acetamido-2-(5-bromo-2-nitrobenzyl)malonate was refluxed in 100 ml. of concentrated hydrochloric acid for 20 hours. After cooling the precipitate was filtered and washed with acetone to give 5.0 g. of the hydrochloride, m.p. 233-234° dec. The latter was converted to the product by treatment with ammonium hydroxide (see Table IV).

5-Chloro-2-nitrophenylalanine Hydrochloride.

In a similar manner as described above a 9.5 g. sample of ethyl 2-acetamido-2-(5-chloro-2-nitrobenzyl)malonate was converted to 5.6 g. of product. An analytical sample was obtained by recrystallization from 95% aqueous ethanol (see Table IV).

5-Methoxy-2-nitrophenylalanine Hydrochloride.

Also, in a manner described above a 5.0 g. sample of ethyl 2-acetamido-2-(5-methoxy-2-nitrobenzyl)malonate (3) was converted to 3.0 g. of product (see Table IV).

Organic Intermediates.

Ethyl 2-Acetamido-2-(5-bromo-2-nitrobenzyl)malonate.

To a solution of 12.6 g. of ethyl acetamidomalonate in 125 ml. of magnesium-dried ethanol containing 1.2 g. of sodium was added 15.1 g. of 5-bromo-2-nitrobenzyl bromide. The reaction mixture was stirred at room temperature for 2 hours after which a liter of water was added to cause precipitation. The precipitate was removed by filtration and dried over phosphorus pentoxide *in vacuo* to yield 17.1 g. (77%) of product, m.p. 143-145°.

Anal. Calcd. for $C_{16}H_{19}BrN_2O_7$: C, 44.56; H, 4.44; N, 6.50. Found: C, 44.31; H, 4.53; N, 6.40.

Ethyl 2-Acetamido-2-(5-chloro-2-nitrobenzyl)malonate.

In a similar manner as described above a 12.5 g. sample of 5-chloro-2-nitrobenzyl bromide was converted to 17.8 g. of product (92%), m.p. 147-148°.

Anal. Calcd. for $C_{16}H_{19}ClN_2O_7$: C, 49.68; H, 4.96; N, 7.24. Found: C, 49.55; H, 5.01; N, 7.16.

5-Bromo-2-nitrobenzyl Bromide.

To a 18.0 g. sample of 5-bromo-2-nitrotoluene dissolved in 45 ml. of anhydrous carbon tetrachloride under reflux conditions was added in increments a total of 14.8 g. of *N*-bromosuccinimide and 1.5 g. of dibenzoyl peroxide over a period of 10 hours. The succinimide was removed by filtration, and the filtrate was passed through an alumina column. Reduction in volume of the solution *in vacuo*, and subsequent chilling resulted in the formation of a precipitate. The latter was filtered and washed with *n*-hexane to give 15.2 g. (62%) of product, m.p. 62-66°.

Anal. Calcd. for $C_7H_5Br_2NO_2$: C, 28.50; H, 1.71; N, 4.75. Found: C, 28.20; H, 1.79; N, 4.41.

5-Chloro-2-nitrobenzyl Bromide.

In a similar manner as described above a 34.0 g. sample of 5-chloro-2-nitrotoluene was converted to 24.5 g. (49%) of product, m.p. 61-62°. An analytical sample was obtained by recrystallization from 95% aqueous ethanol.

Anal. Calcd. for $C_7H_5BrClNO_2$: C, 33.57; H, 2.01; N, 5.59. Found: C, 33.27; H, 2.10; N, 5.41.

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