Synthesis and Properties of 3-Chloro- and 3,7-Dichloro-3,4-dihydro-1-hydroxycarbostyrils and Related Heterocyclic Compounds

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3-Chloro- and 3,7-dichloro-3,4-dihydro-1-hydroxycarbostyrils were synthesized by the catalytic hydrogenation of the α-chloro- and α,4-dichloro-β-(*o*-nitrophenyl)propionic acids in strong acidic solution over platinum-on-carbon sulfided catalyst. However, the catalytic hydrogenation of α-bromo-β-(*o*-nitrophenyl)propionic acid yielded 3,4-dihydro-1-hydroxycarbostyril under the same experimental conditions. The 3-chloro-3,4-dihydro-1-hydroxycarbostyril and the α-chloro-β-(*o*-nitrophenyl)propionic acid underwent facile dehydrochlorination in mild alkaline solution to give 1-hydroxycarbostyril and *o*-nitrocinnamic acid, respectively. Selective reduction of 3-chloro-3,4-dihydro-1-hydroxycarbostyril and 1-hydroxycarbostyril to the corresponding lactams, 3-chloro-3,4-dihydrocarbostyril and carbostyril, was effected by catalytic hydrogenation in hydrochloric acid over platinum black catalyst. The structures of the substituted carbostyril derivatives were correlated with their proton nmr spectra.

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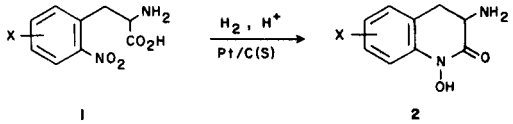
We reported previously [1,2] that the catalytic hydrogenation of halo-substituted *o*-nitrophenylalanines (**1**) in acidic solution over platinum-on-carbon sulfided catalyst gives the corresponding halo-substituted 3-amino-3,4-dihydro-1-hydroxycarbostyrils (**2**) in good yields without



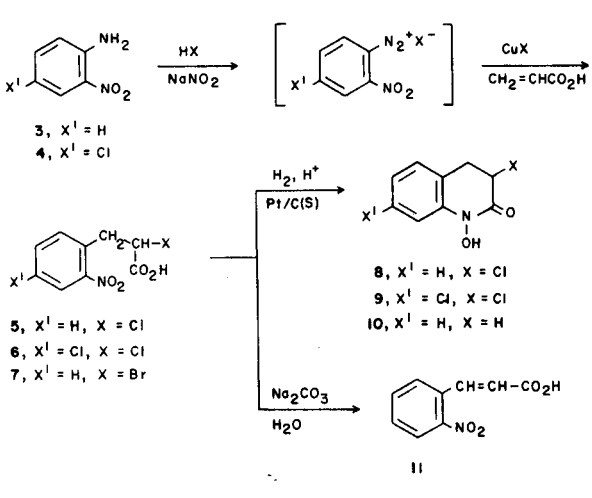
1 2

hydrogenolysis of the aromatic carbon-to-halogen bond. These halogenated cyclic hydroxamic acids **2** have been shown to have potent antimicrobial activities [2-4] and to undergo acid-catalyzed nucleophilic rearrangements [1,5].

Because of our continued interest in the chemistry of various substituted carbostyrils, we subjected a group of α-halo-β-(*o*-nitrophenyl)propionic acids to catalytic hydrogenation with the aim of finding an entry to 3-halo-substituted 3,4-dihydro-1-hydroxycarbostyrils which contain the halogens aliphatically bonded at the 3-position of the heterocyclic ring. To our knowledge, no study on the synthesis of α-halocyclic hydroxamic acids has appeared in the chemical literature. Therefore, the purpose of this paper is to describe the synthesis and properties of these 3-chloro-substituted 3,4-dihydro-1-hydroxycarbostyrils and related heterocyclic compounds which were obtained by catalytic hydrogenation of α-halo-β-(*o*-nitrophenyl)propionic acids.

For the purpose of this preliminary study, the α-chloro, α-bromo- and α,4-dichloro-substituted β-(*o*-nitrophenyl)-propionic acids were synthesized by the Meerwein arylation reaction as shown in Scheme I. *o*-Nitroaniline (**3**) and 4-chloro-2-nitroaniline (**4**) were diazotized with nitrous acid in the usual manner to give the intermediate *o*-nitrobenzenediazonium chlorides which were condensed with acrylic acid in the presence of cuprous chloride and hydrochloric acid to yield α-chloro-β-(*o*-nitrophenyl)propionic acid (**5**) and α,4-dichloro-β-(2-nitrophenyl)propionic acid (**6**), respectively. In the presence of hydrobromic acid and cuprous bromide, acrylic acid was arylated by the *o*-nitrobenzenediazonium bromide to afford the corresponding α-bromo-β-(*o*-nitrophenyl)propionic acid (**7**) in low yield. These α-halo acids were isolated from the reaction mixtures initially as oils which crystallized as yellow solids from formic acid.

SCHEME I



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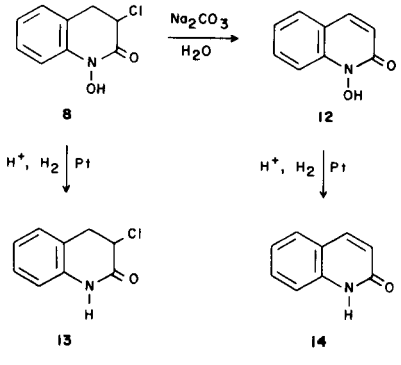
Each of the α-halo acids was catalytically hydrogenated in methanolic hydrochloric acid over platinum-on-carbon sulfided catalyst at a hydrogen pressure of 55 psig for 1.5-2 hours. As depicted in Scheme I, the two α-chloro-

propionic acids, **5** and **6**, underwent reductive cyclization to the corresponding 3-chloro-3,4-dihydro-1-hydroxycarbostyril (**8**) and 3,7-dichloro-3,4-dihydro-1-hydroxycarbostyril (**9**), respectively. In contrast to these results, the α-bromopropionic acid **7** underwent catalytic debromination as well as reductive cyclization to give 3,4-dihydro-1-hydroxycarbostyril (**10**) as the sole product. Unlike the solubility behavior of the 3-aminocarbostyrils **2** which form quaternary salts in aqueous acidic solution, the 3-chloro- and 3,7-dichloro- derivatives of 3,4-dihydro-1-hydroxycarbostyril are insoluble in aqueous solution, but are soluble in alcohols, acetone, and chloroform. These α-chloro cyclic hydroxamic acids were characterized by microchemical and spectral analyses.

It was found that facile dehydrochlorination of both α-chloro-β-(*o*-nitrophenyl)propionic acid **5** and 3-chloro-3,4-dihydro-1-hydroxycarbostyril **8** occurs in refluxing aqueous sodium carbonate to yield *o*-nitrocinnamic acid (**11**)

SCHEME II



as shown in Scheme I and 1-hydroxycarbostyril (**12**) as shown in Scheme II, respectively. The infrared spectra of *o*-nitrocinnamic acid (**11**) and 1-hydroxycarbostyril (**12**) were identical to those of authentic samples of the compounds obtained commercially.

In a separate experiment, the 3-chlorohydroxamic acid **8** was catalytically hydrogenated in methanolic hydrochloric acid over platinum black catalyst at a hydrogen pressure of 55 psig for 3 hours to yield the corresponding lactam, 3-chloro-3,4-dihydrocarbostyril (**13**) as depicted in Scheme II. Under the same conditions of catalytic hydrogenation, deoxygenation of 1-hydroxycarbostyril (**12**) also occurred to afford carbostyril (**14**) as shown in Scheme II.

The structures of the various reductive cyclization products prepared in this study were correlated with their proton nmr spectra. The two magnetically non-equivalent benzylic protons at C-4 and the methinyl proton at C-3 of the 3-chloro-substituted cyclic hydroxamic acids showed a characteristic ABX splitting pattern. For both compounds **8** and **9** in deuterated acetone, the benzylic protons, which are the AB portion of the spectra, appeared as two symmetrical quartets in the δ 7.9-8.9 range with the inner peaks possessing much greater intensities than the outer peaks. Since the vicinal coupling constants ($^3J_{AX} = {}^3J_{BX} = 4.5$ Hz) between the methinyl proton and the benzylic protons were the same, the absorption of the methinyl proton, which is the X portion of the spectra, appeared as a deceptively simple triplet centered at δ ~4.8. Another characteristic of the nmr spectra of the α-chloro cyclic hydroxamic acids was the large geminal coupling constants ($^2J_{AB} = -15$ Hz) for the benzylic protons. As expected, the aromatic splitting patterns of these heterocycles were different. The 3-chloro compound **8** showed a complex ABCD system in the δ 3.2-4.9 range, while the 3,7-dichloro compound **9** showed a characteristic ABCD system in the δ 2.9-3.5 range.

The nmr spectra of the other carbostyril derivatives prepared in this study were also correlated with their structures. The spectrum of 3,4-dihydro-1-hydroxycarbostyril **12** in deuterated acetone showed a complex symmetrical AA'BB' system in the δ 2.4-3.2 range for the ethylenic protons of C-4 and C-3, while the spectrum of 1-hydroxycarbostyril **13** in dimethyl sulfoxide showed two doublets for the olefinic protons δ 6.75 and δ 7.9 ($J_{AB} = 9$ Hz). The olefinic proton at C-4 of **13** appears farther downfield than the proton at C-3. The nmr absorption patterns of the lactams **13** and **14** were similar to those of the corresponding cyclic hydroxamic acids with the exception of the absorption of the amide proton in the δ 0.5 range.

The results of this investigation demonstrates that certain *o*-nitroaromatic α-chloro acids are converted directly to the corresponding cyclic α-chlorohydroxamic acids by catalytic hydrogenation without hydrogenolysis of the aliphatic carbon-to-chlorine bond. For the selective reduction and cyclization, the choice of conditions is platinum-on-carbon sulfided catalyst in strong acidic solution. on the other hand, the lability of bromine relative to chlorine under these conditions of catalytic hydrogenation was also shown by concominant debromination of α-bromo-β-(*o*-nitrophenyl)propionic acid (**7**) during its reductive cyclization leading to 3,4-dihydro-1-hydroxycarbostyril (**10**). These results are in accord with those of other investigators who have found that the ease of removal of halogen by catalytic hydrogenation is related inversely to the carbon-to-halogen bond strength [6].

It was also found that cyclic hydroxamic acids containing chloro and olefinic groups were selectively reduced to the corresponding functionalized lactams by catalytic hydrogenation using platinum black catalyst and hydrochloric acid. Under these conditions of catalytic hydrogenation, neither the carbon-to-chlorine nor the carbon-to-carbon bonds are reduced in these heterocyclic structures, and only the nitrogen-to-oxygen bond of the hydroxamate function is susceptible to hydrogenolysis.

In conclusion, this work further demonstrates that cata-

lytic hydrogenation is a useful and often preferred method in preparative heterocyclic chemistry.

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 deuterated chloroform and acetone as solvents and tetramethylsilane (TMS) as the internal standard. The ir and nmr spectra of all compounds reported are consistent with their proposed structures. Pertinent nmr data are presented in the discussion section. Microanalyses were performed by M-H-W Laboratories, Phoenix, Arizona.

α-Chloro-β-(*o*-nitrophenyl)propionic Acid (**5**).

To a solution of 6.91 g (0.0500 mole) of *o*-nitroaniline dissolved in 100 ml of acetone and 21 ml of concentrated hydrochloric acid was added a solution of 3.45 g (0.0510 mole) of sodium nitrite in 25 ml of water at a temperature below 8°. To the reaction mixture was added 50 ml of acrylic acid followed by 500 mg of cuprous chloride in small increments. Acetone was removed from the reaction mixture *in vacuo*, and the solid was removed by filtration. The filtrate was treated with 200 ml of water, and the aqueous solution was chilled at 0° for 20 hours. The oil which separated from the aqueous phase was extracted with ether. After removal of the ether *in vacuo*, the oily residue was dissolved in aqueous sodium bicarbonate solution and extracted successively with 75 ml of chloroform and ether. The aqueous layer was separated, decolorized with charcoal, acidified with hydrochloric acid, and extracted with 300 ml of benzene. The removal of benzene *in vacuo* gave a residue which was recrystallized from formic acid to give 5.0 g (44%) of the pale yellow crystalline product, mp 108-109°.

Anal. Calcd. for $C_9H_8ClNO_4$: C, 47.08; H, 3.51; N, 6.10. Found: C, 47.23; H, 3.75; N, 5.82.

α,4-Dichloro-β-(2-nitrophenyl)propionic Acid (**6**).

To a 8.27 g (0.0480 mole) sample of 4-chloro-2-nitrotoluene dissolved in 100 ml of acetone was added 22 ml of concentrated hydrochloric acid followed by a solution of 3.45 g (0.051 mole) of sodium nitrite in 10 ml of water while keeping the temperature of the solution below 8°. Then 50 ml of acrylic acid was added followed by the addition of 400 mg of cuprous chloride in small increments. The volume of the reaction mixture was reduced *in vacuo*, and water was added to give 6.53 g (52%) of product. Successive recrystallizations from toluene and butanol gave an analytical sample, mp 149-150°.

Anal. Calcd. for $C_9H_7Cl_2NO_4$: C, 40.94; H, 2.67; N, 5.30. Found: C, 40.81; H, 2.66; N, 5.37.

α-Bromo-β-(*o*-nitrophenyl)propionic Acid (**7**).

In a manner similar to that used for the synthesis of **5**, a 6.91 g (0.0500) sample of *o*-nitroaniline was converted to 3.65 g (27%) of **6**. Hydrobromic acid and cuprous bromide were used instead of hydrochloric acid and cuprous chloride, respectively. Recrystallization from toluene gave an analytical sample, mp 112-114°.

Anal. Calcd. for $C_9H_8BrNO_4$: C, 39.44; H, 2.94; N, 5.11. Found: C, 39.38; H, 2.97; N, 5.06.

3-Chloro-3,4-dihydro-1-hydroxycarbostyril (**8**).

A 1.0 g (0.0043 mole) sample of **5** suspended in 6 ml of 50% aqueous methanol and one ml of concentrated hydrochloric acid was hydrogenated at 3.67 kg/cm² of hydrogen pressure in the presence of 100 mg of 5% Pt on C/sulfided catalyst for 1-2 hours. The catalyst was removed by filtration and the volume of the resulting solution was reduced *in vacuo* to an oil. The latter was crystallized in cold ether to yield 0.59 g (69%) of product. Recrystallization from methanol-ether gave an analytical sample mp 126-128°.

Anal. Calcd. for $C_9H_8ClNO_2$: C, 54.70; H, 4.08; N, 7.09; Cl, 17.94. Found: C, 54.94; H, 4.29; N, 6.97; Cl, 17.73.

3,7-Dichloro-3,4-dihydro-1-hydroxycarbostyril (**9**).

Under similar conditions as used for the synthesis of **8**, a 1.0 g (0.0038 mole) sample of **6** was hydrogenated to give 0.29 g (33%) of product, mp 136-138°.

Anal. Calcd. for $C_9H_7ClNO_2$: C, 46.58; H, 3.04; N, 6.04; Cl, 30.55. Found: C, 46.32; H, 3.07; N, 5.84; Cl, 30.31.

3,4-Dihydro-1-hydroxycarbostyril (**10**).

A 1.0 g (0.0036 mole) sample of **7** was hydrogenated as described above for the synthesis of **8** to give 0.22 g (38%) of product. Recrystallization from acetone-hexane gave an analytical sample, mp 113-117°.

Anal. Calcd. for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.53. Found: C, 66.53; H, 5.46; N, 8.41.

o-Nitrocinnamic Acid (**11**).

A 25 ml aqueous solution of 1.0 g (0.0043 mole) of **5** and 1.0 g sodium carbonate was refluxed for 9 hours. The solution was treated with hydrochloric acid to about *p*H 1 and a precipitate formed. The mixture was extracted with 200 ml of ether, and the extract was treated with anhydrous sodium sulfate. After removal of the drying agent by filtration, the volume of the filtrate was reduced *in vacuo* to give 0.35 g (39%) of product. Recrystallization from ethyl acetate gave a product, mp 239-241°, which compares to a literature value of 243-245° [7]. Infrared and nuclear magnetic resonance spectra of the product were identical to that of an authentic sample.

1-Hydroxycarbostyril (**12**).

A 0.25 g (0.0013 mole) sample of **8** and 0.25 g of sodium carbonate in 10 ml of water were refluxed for 6 hours. The solution was acidified by treatment with hydrochloric acid to a *p*H 1 to precipitate 0.17 g (83%) of crude product. Recrystallization from acetone gave an analytical sample, mp 183-185°.

Anal. Calcd. for $C_9H_7NO_2$: C, 67.08; H, 4.38; N, 8.69. Found: C, 66.88; H, 4.31; N, 8.64.

3-Chloro-3,4-dihydrocarbostyril (**13**).

A 0.50 g (0.0025 mole) sample of **8** in 6 ml of 50% aqueous methanol and one ml of concentrated hydrochloric acid was hydrogenated at 3.67 kg/cm² of hydrogen pressure in the presence of 50 mg of Pt black catalyst for 3 hours. The catalyst was removed by filtration, the volume of the filtrate was reduced *in vacuo*, and cold ether was added to give 0.10 g (22%) of product, mp 177-179°. This product gave a negative ferric chloride test for hydroxamates.

Anal. Calcd. for C_9H_8ClNO: C, 59.52; H, 4.44; N, 7.71; Cl, 19.52. Found: C, 59.54; H, 4.67; N, 7.70; Cl, 19.48.

Carbostyril (**14**).

A 0.25 g (0.0015 mole) sample of **12**, dissolved in 25 ml of ethanol, was hydrogenated at 3.67 kg/cm² hydrogen pressure in the presence of 24 mg of 5% Pt on C catalyst for 2 hours. The catalyst was removed by filtration and the volume of the filtrate was reduced *in vacuo* to give 0.17 g (78%) of product. Recrystallization from methanol gave a product, mp 194-196°, which compares with a literature value of 199-200° [8]. The infrared spectrum of the product was identical to that of an authentic sample.

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