Synthesis of Some 7-Substituted 3-Chloro-3,4-dihydro-1-hydroxycarbostyrils by the Reduction Cyclization of α-Chloro-β-(4-substituted-2-nitrophenyl)propionic Acids

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A new method was developed for the synthesis of some 7-substituted 3-chloro-3,4-dihydro-1-hydroxycarbostyrils 3c-g in which α-chloro-β-(4-substituted-2-nitrophenyl)propionic acids **2c-g** were reductively cyclized by catalytic hydrogenation over platinum-on-carbon sulfided catalyst. In particular, this method was applied to α-chloro-β-(2-nitrophenyl)propionic acids bearing 4-methyl **2c**, 4-ethyl **2d**, 4-ethoxy **2e**, 4-(*n*-butyl **2f** and 4-phenyl **2g** substituents to afford good yields of the corresponding 7-methyl **3c**, 7-ethyl **3d**, 7-ethoxy **3e**, 7-(*n*-butyl) **3f**, and 7-phenyl **3g** substituted 3-chloro-3,4-dihydro-1-hydroxycarbostyrils. The various 4-substituted α-chloro-β-(2-nitrophenyl)propionic acids **2c-q** were synthesized by reacting the *in situ* diazotized salts of the appropriate 4-substituted-2-nitroanilines in aqueous acetone with acrylic acid in the presence of cuprous chloride and hydrochloric acid. All compounds prepared in this study were characterized by microanalytical and ir and nmr spectral data.

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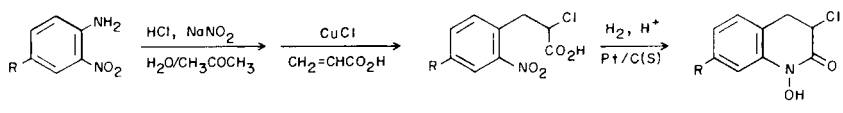
Previously we found that the catalytic hydrogenation of α-chloro and α,4-dichloro-β-(2-nitrophenyl)propionic acids **2a** and **2b** in acidic solution over platinum-on-carbon sulfided catalyst yielded 3-chloro- and 3,7-dichloro-3,4-dihydro-1-hydroxycarbostyrils **3a** and **3b**, respectively, without hydrogenolysis of the C-Cl bonds [1]. To our knowledge, this was the first report of the synthesis of cyclic α-chlorohydroxamic acids by the selective reduction and cyclization of *o*-nitroaromatic α-chloro acids. Our continued interest in this area of heterocyclic chemistry [2-11] has led us to a further study of this synthetic method by preparing and catalytically hydrogenating a group of 4-substituted α-chloro-β-(2-nitrophenyl)propionic acids **2c-g**. In the present paper, we present the results of this study in which the 7-substituted 3-chloro-3,4-dihydro-1-hydroxycarbostyrils **3c-g** were obtained and characterized as the heterocyclic products.

For the purpose of our study, the 4-methyl **2c**, 4-ethyl **2d**, 4-ethoxy **2e**, 4-(*n*-butyl) **2f**, and the 4-phenyl **2g** substituted α-chloro-β-(2-nitrophenyl)propionic acids were synthesized by the Meerwein arylation of acrylic acid in aqueous acetone with the *in situ* diazotized 4-substituted 2-nitroanilines **1c-g** in the present of cuprous chloride and hydrochloric acid as shown in Scheme I. The usual conditions for the arylation reaction was 5°, however, a high yield (85%) of the α-chloro-β-[4-(*n*-butyl)-2-nitrophenyl]-propionic acid (**2f**) was obtained only when the diazotization step of 4-(*n*-butyl)-2-nitroaniline (**1f**) was carried out at 15°. The requisite 4-substituted 2-nitroanilines **1c-f** were available from commercial sources with the exception of the 4-(*n*-butyl)-2-nitroaniline (**2f**). The latter compound was conveniently prepared by nitration of *p*-(*n*-butyl)acetanilide followed by acid hydrolysis as previously reported [12].

Catalytic hydrogenation of the various α-chloro-β-(4-substituted-2-nitrophenyl)propionic acids **2c-g** in strongly acidic aqueous methanol over platinum-on-carbon sulfided catalyst gave the corresponding 7-substituted-3-chloro-3,4-dihydro-1-hydroxycarbostyrils **3c-g** as shown in Scheme I. These cyclic α-chlorohydroxamic acids **3c-g** were obtained in good yields as the sole heterocyclic products. Their yields and physical constants are compiled in Table II. Each of the products gave the typical ferric complex test (violet) for hydroxamic acids when treated with ferric chloride reagent.

SCHEME I



1a–g 2a–g 3a–g

1,2,3	a	b	c	d	e	f	g
R	H	Cl	CH_3	C_2H_5	OC_2H_5	n-C_4H_9	C_6H_5

Table I

Experimental Data of α-Chloro-β-2-nitrophenyl-4-(substituted)propionic Acids, **2c-g**, Prepared

Compound No.	R-	Yield %	Mp °C	Solvents [a] of Crystallization	Composition	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
2c	CH_3	57	173-174	HCO_2H	$C_{10}H_{10}NO_4Cl$	49.30	49.50	4.14	4.23	5.75	5.59
2d	C_2H_5	85	127-128	$CHCl_3/C_6H_{14}$	$C_{11}H_{12}NO_4Cl$	51.27	51.53	4.69	4.79	5.44	5.23
2e	C_2H_5O	47	103-105	$CHCl_3$/PE	$C_{11}H_{12}NO_5Cl$	48.28	48.35	4.42	4.45	5.12	5.08
2f	n-C_4H_9	85	87-88	$CHCl_3$/PE	$C_{13}H_{16}NO_4Cl$	54.65	54.82	5.64	5.61	4.90	4.75
2g	C_6H_5	65	137-138	PE	$C_{15}H_{12}NO_4Cl$	58.93	59.06	3.96	3.78	4.58	4.80

[a] PE = petroleum ether.

Table II

Experimental Data of 3-Chloro-3,4-dihydro-1-hydroxycarbostyrils, **3c-g**, Prepared

Compound No.	R-	Yield %	Mp °C	Solvents [a] of Crystallization	Composition	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
3c	CH_3	78	167-172	CH_3OH	$C_{10}H_{10}NO_2Cl$	56.75	56.79	4.76	4.86	6.62	6.56
3d	C_2H_5	75	113-114	CH_3COCH_3	$C_{11}H_{12}NO_2Cl$	58.54	58.61	5.36	5.25	6.21	6.26
3e	C_2H_5O	78	113-115	C_2H_5OH	$C_{11}H_{12}NO_3Cl$	54.67	54.83	5.01	5.06	5.80	5.80
3f	n-C_4H_9	87	88-89	$CHCl_3$/PE	$C_{13}H_{16}NO_2Cl$	61.54	61.77	6.36	6.39	5.52	5.43
3g	C_6H_5	90	151-152	$CHCl_3$/PE	$C_{15}H_{12}NO_2Cl$	65.82	65.98	4.42	4.45	5.12	5.14

[a] PE = petroleum ether.

Table III

Spectral Data of Prepared Compounds **2c-g**

Compound No.	IR (potassium bromide) cm^{-1} ν C=O	ν NO_2	^{1}H NMR [a] (deuteriochloroform/-TMS internal, 60 Hz) δ (ppm)
2c	1725	1520 1345	(in acetone-d_6) 2.4 (s, 3H, CH_3), 3.2-3.9 AB part of ABX (m, 1H, J_{AB} = 14 Hz, β-CH_2), 4.7 X part of ABX (dd, 1H, J_{AX} = 6 Hz and J_{AB} = 8 Hz, α-CH), 7.4-7.8 (m, 3H, H arom), 10.0 (s, 1H, -CH_2H)
2d	1725	1520 1340	1.3 (t, 3H, J = 8 Hz, CH_3), 7.5 (q, 2H, J = 8 Hz, CH_3CH_2-), 3.1-3.9 AB part of ABX (m, 2H, J_{AB} = 14 Hz, β-CH_2), 4.7 X part of ABX (dd, 1H, J_{AX} = 6 Hz and J_{BX} = 8 Hz, α-CH), 7.2-7.9 (m, 3H, H arom), 10.2 (s, 1H, -CO_2H)
2e	1733	1529 1355	1.4 (t, 3H, J = 8 Hz, CH_3), 3.1-3.9 AB part of ABX (m, 2H, J_{AB} = 14 Hz, β-CH_2), 4.1 (q, 2H, J = 8 Hz, CH_2CH_2O-), 4.7 X part of ABX (dd, 1H, J_{AX} = 6 Hz and J_{BX} = 8 Hz, α-CH), 7.0-7.7 (m, 3H, H arom), 8.85 (s, 1H, -CO_2H)
2f	1740	1525 1345	0.45 (t, 3H, J = 6 Hz, CH_3), 0.5-1.0 [m, 4H, $CH_3(CH_2)_2CH_2$-], 3.5 (t, 2H, J = 8 Hz, 4-CH_2-Ar), 3.1-4.0 AB part of ABX (m, 2H, J_{AB} = 14 Hz, β-CH_2), 4.7 X part of ABX (dd, 1H, J_{AX} = 6 Hz and J_{BX} = 8 Hz, α-CH), 7.2-8.0 (m, 3H, H arom), 10.6 (s, 1H, -CO_2H)
2g	1715	1530 1340	3.2-4.1 AB part of ABX (m, 2H, J_{AB} = 14 Hz, β-CH_2), 4.8 X part of ABX (dd, 1H, J_{AX} = 6 Hz and J_{BX} = 8 Hz, α-CH), 7.2-8.0 (m, 8H, H arom), 10.6 (s, 1H, -CO_2H)

[a] This solvent was used for all compounds except **2c**.

Table IV

Spectral Data of Prepared Compounds **3c-g**

Compound No.	IR (potassium bromide) cm^{-1} ν C=O	^{1}H NMR (Solvent/TMS internal), δ (ppm)
3c	1660	(deuteriochloroform) 2.3 (s, 3H, CH_3), 2.8-3.8 AB part of ABX (m, 2H, J_{AB} = 17 Hz, 4-CH_2), 4.9 X part of ABX (t, 1H, J_{AX} = J_{BX} = 4 Hz, 3-CH), 6.7-7.5 (m, 3H, H arom)
3d	1640	(deuteriochloroform/DMSO-d_6) 1.25 (t, 3H, J = 7 Hz, CH_3), 2.65 (q, 2H, J = 7 Hz, 7-CH_2CH_3), 2.8-3.7 AB part of ABX (m, 2H, J_{AB} = 17 Hz, 4-CH_2), 4.75 (t, 1H, J_{AX} = J_{BX} = 4.5, 3-CH), 6.8-7.4 (m, 3H, H arom)
3e	1678	(deuteriochloroform) 1.45 (t, 3H, J = 7.5 Hz, CH_3), 2.8-3.7 AB part of ABX (m, 2H, J_{AB} = 17 Hz, 4-CH_2), 4.1 (q, 2H, J = 7.5, -CH_2O), 4.75 X part of ABX (m, 1H, J_{AX} = J_{BX} = 5 Hz, 3-CH), 6.5-7.35 (m, 3H, H arom)
3f	1650	(deuteriochloroform/DMSO-d_6) 0.9 (t, 3H, J = 6 Hz, -CH_3), 1.1-1.9 (m, 4H, $CH_3(CH_2)_2$-), 2.6 (t, 2H, J = 7 Hz, 7-CH_2-), 2.8-3.7 AB part of ABX (m, 2H, J_{AB} = 17 Hz, 4-CH_2), 4.7 (t, 1H, J_{AX} = J_{BX} = 5 Hz, 3-CH), 6.7-7.4 (m, 3H, H arom)
3g	1650	(deuteriochloroform/DMSO-d_6) 2.9-3.7 AB part of ABX (m, 2H, J_{AB} = 17 Hz, 4-CH_2), 4.75 X part of ABX (t, 1H, J_{AX} = J_{BX} = 5 Hz, 3-CH), 7.1-7.8 (m, 8H, H arom)

The selected ir data (Table III and IV) showed that the C=O stretching frequencies of the 4-substituted α-chloro-β-(2-nitrophenyl)propionic acids **2c-g** occur at higher frequencies, 1715-1740 cm^{-1} region, than the corresponding

C=O frequencies of the 7-substituted 3-chloro-3,4-dihydro-1-hydroxycarbostyrils **3c-g** which absorb in the 1640-1680 cm^{-1} region. As would be expected, the strong intensities of the asymmetric and symmetric N=O stretching frequencies in the 1520-1530 and 1340-1355 cm^{-1} regions, respectively, were observed only for the nitro groups of compounds **2c-g** (Table III).

The nmr spectra of both types of α-chloro-substituted compounds, **2c-g** and **3c-g**, showed characteristic ABX splitting patterns as indicated in Tables III and IV. The AB part of the ABX pattern which appeared as two overlapping quartets in the δ 2.8-4.0 range was common to each type of compound due to the two diastereotopic benzyl protons. However, the geminal coupling constants of these protons, J_{AB} = 17 Hz, in the heterocyclic products **3c-g** were consistently larger than those, J_{AB} = 14 Hz, in the open-chain compounds **2c-g**. Even though the X part of the ABX pattern for each of the compounds appeared in the same region, δ 4.7-4.8, due to the methinyl proton, the splitting patterns and the vicinal coupling constants were different for the two types of compounds. The δ_X signal appeared as a doublet of a doublet with different vicinal coupling constants, J_{AX} = 6 Hz and J_{BX} = 8 Hz, in the α-chloro acids **2c-g**, while the signal appeared as a triplet with identical vicinal coupling constants, $J_{AX} = J_{BX}$ = 4.5-5 Hz, in the 7-substituted 3-chloro-3,4-dihydro-1-hydroxycarbostyrils **3c-g**. These spectral features were useful in the identity of the cyclic α-chlorohydroxamic acids **3c-g** and the *o*-nitroaromatic acids **2c-g** from which they were derived.

In summary, we have demonstrated a new method of general applicability for the synthesis of some 7-substituted 3-chloro-3,4-dihydro-1-hydroxycarbostyrils directly from the corresponding α-chloro-β-(4-substituted-2-nitrophenyl)propionic acids by catalytic hydrogenation in acidic methanol over platinum-on-carbon sulfided catalyst. The advantage of this method is that it consists of only two reaction steps from readily available starting materials, and it results in the selective reduction of the nitro group without affecting the α-chloro group on account of the platinum-on-carbon sulfided catalyst. Moreover, the mild hydrogenation conditions, the good yields, and the purity of the heterocyclic products makes the present synthesis a convenient method to obtain previously unknown cyclic α-chlorohydroxamic acids for both chemical and biological studies.

EXPERIMENTAL

General.

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman Acculab 4 dual beam spectrophotometer (potassium bromide) and were calibrated with polystyrene film. Nuclear magnetic resonance spectra were obtained with a Perkin-Elmer R-12B spectrophotometer at 60 MHz using deuterated chloroform, dimethylsulfoxide, or mixtures thereof, as solvents with tetramethylsilane (TMS) as the internal standard. Spectral data of compounds prepared in this study are presented in Tables III and IV. Microanalyses were performed by M-H-W Laboratories, Phoenix, Arizona.

4-(Substituted)-2-nitroanilines **1c-g**.

4-Methyl-2-nitroaniline (**1c**), 4-ethyl-2-nitroaniline (**1d**), 4-ethoxy-2-nitroaniline (**1e**), and 4-amino-2-nitrobiphenyl (**1g**) were purchased from Aldrich Chemical Company, Milwaukee, Wisconsin. 4-(*n*-Butyl)-2-nitroaniline (**1f**) was prepared by acid hydrolysis of the corresponding 4-(*n*-butyl)-2-nitroacetanilide obtained by nitration of *p*-(*n*-butyl)acetanilide according to a previously reported procedure [12].

α-Chloro-β-(4-substituted-2-nitrophenyl)propionic Acids, **2c-g**. General Procedure.

These compounds were prepared by patterning the procedure used previously for the synthesis of **2a** and **2b** [1] with modifications denoted for specific compounds. A cold solution (15 ml) of 33% sodium nitrite (w/v) was gradually added to a solution of the 4-substituted-2-nitroaniline (0.022 mole) dissolved in acetone (60 ml) and concentrated hydrochloric acid (30 ml) with stirring below 5°. In the case of the 4-(*n*-butyl)-2-nitroaniline (**1f**), this addition to form the diazonium salt was maintained at 15° for the optimal yield. Then, acrylic acid (10 ml) was added, followed by the addition of small increments of solid cuprous chloride (~50 mg) until evolution of nitrogen ceased while keeping the temperature below 5°. After evaporation of the acetone under reduced pressure followed by the removal of the insoluble salts by filtration, cold water (50 ml) was added to the filtrate to precipitate the crude α-chloro acid as an oil. In the case of α-chloro-β-(4-ethyl-2-nitrophenyl)propionic acid (**2d**), the oil crystallized at this stage upon cooling and the desired product **2d** was recovered by filtration. The other oils which failed to crystallize were extracted with ether (3 × 100 ml). The ether extracts were combined and taken to a residual oil by evaporation of the ether under reduced pressure. The residue was dissolved in the least amount of a saturated solution by the aqueous sodium carbonate and then the solution was taken to a *p*H of 3 by the dropwise addition of concentrated hydrochloric acid. The acidified mixture was extracted with ether or chloroform (3 × 50 ml). The extracts were combined, washed with water (2 × 50 ml), separated and dried over anhydrous sodium sulfate. After removing the drying agent by filtration, the filtrate was taken to dryness by removal of the ether under reduced pressure. The residue was crystallized from the solvents given in Table I. The melting points and analytical data of the various substituted α-chloro acids **2c-g** are also given in Table I. The ir and nmr spectral data of these products are listed in Table III.

7-(Substituted)-3-chloro-3,4-dihydro-1-hydroxycarbostyrils **3c-g**. General Procedure.

A suspension of 1.0 g of the α-chloro acids **2c-g** in 6 ml of 50 percent aqueous methanol and 1 ml of concentrated hydrochloric acid was hydrogenated in the presence of 100 mg of platinum-on-carbon sulfided catalyst at 3.67 kg/cm^2 of hydrogen pressure for 3 hours by the use of a low-pressure Parr hydrogenation apparatus. The catalyst was removed by filtration and the volume of the filtrate was reduced *in vacuo* to leave an oil. The oils at this stage were crystallized from solvent mixtures given in Table II. Further recrystallization of the products **3c-g** from the solvent mixtures (Table II) afforded analytical samples which gave a positive hydroxamate test (violet) with ferric chloride reagent. Melting points and analytical data are presented in Table II while ir and nmr spectral data are given in Table IV.

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