

Synthesis of 4-Hydroxy-2-methylisocarbostyryl-3-carboxanilides

Joseph G. Lombardino

Medical Research Laboratories, Pfizer, Inc.

A procedure for preparing the title compounds is reported. These compounds represent the first 2-substituted-4-hydroxyisocarbostyryls, a structural type which could not be obtained by *N*-alkylation of the previously known 2*H*-4-hydroxyisocarbostyryl. Although 3-carboxanilides in this series could not be made by aminolysis of the corresponding 3-ester, they were successfully prepared from 4-hydroxy-2-methylisocarbostyryl using aryl isocyanates and sodium hydride in hexamethylphosphoramide as solvent. Evidence is presented for an enolic ("4-hydroxy") form of the title compounds and preference for *O*-alkylation was observed. Contrary to previous reports, data was obtained to support the enolic structure of the previously known 4-hydroxyisocarbostyryl.

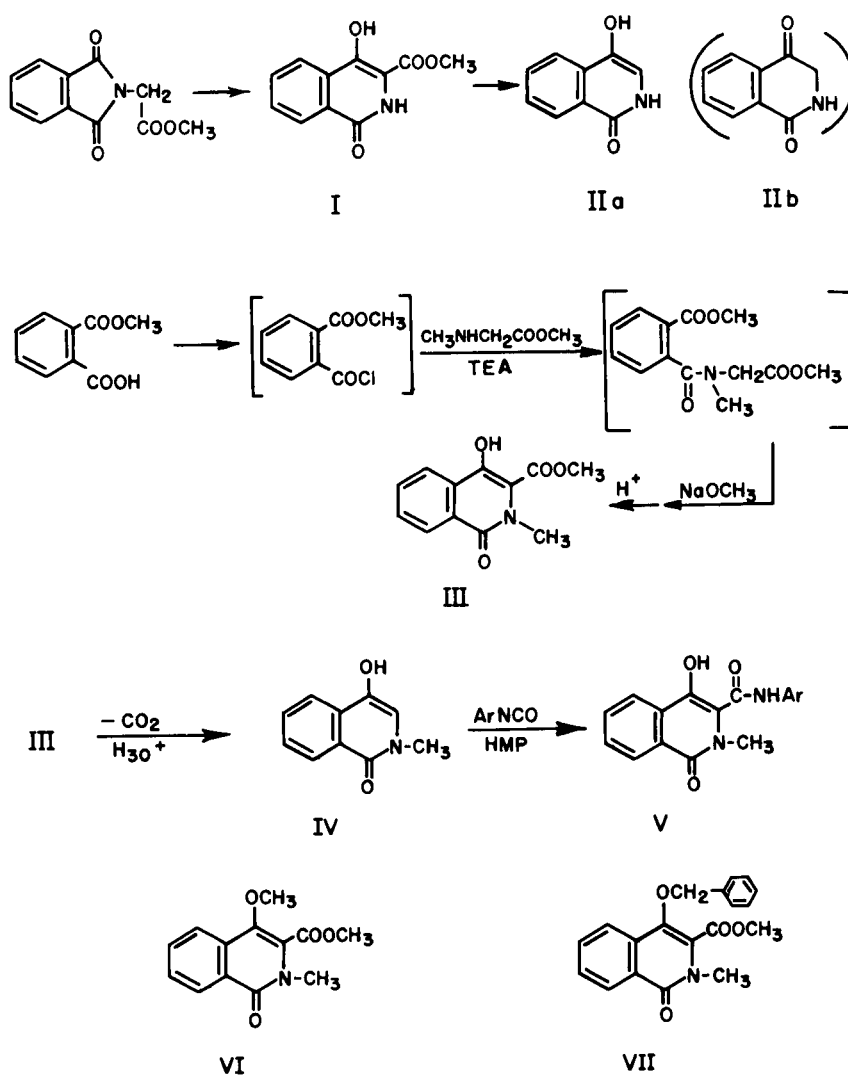
In 1900, Gabriel and Colman (1) reported the rearrangement of methyl phthalimidoacetate to 4-hydroxyisocarbostyryl-3-carboxylic acid, methyl ester (I) in the presence of sodium methoxide. Acid catalyzed decarboxylation of I was reported to give 4-hydroxyisocarbostyryl (II). Since the initial work, Hill (2) has discussed the mechanism of the rearrangement which produces II and Caswell (3) has offered evidence for the existence of II as the 1,4-dione structure (IIb). Analogous applications of the Gabriel-Colman rearrangement to substituted phthalimides are also known (4-7), and two other synthetic approaches to 4-hydroxyisocarbostyryls have been described (8,9). No 2-alkyl-4-hydroxyisocarbostyryls appear to be known, however.

In connection with a continuing study of the biological activity of heterocyclic β -ketoamides, it became desirable to prepare some 4-hydroxy-2-methylisocarbostyryl-3-carboxanilides. Aminolysis of the known ester I followed by *N*-methylation appeared to offer the most direct route to such compounds. However, all attempts to cause I to react with aniline in solvents such as refluxing xylene or hot dimethylformamide resulted only in the recovery of I. In refluxing tetralin, I was decomposed in the presence of aniline to a complex mixture of products. Attempts to prepare the ester III by *N*-alkylation of I with methyl iodide in the presence of base repeatedly produced a complex mixture of products (thin-layer chromatographic evidence) which could not be separated but is assumed to consist of *N*- and *O*-methylated as well as *N,O*-dimethylated products. When two equivalents of base and an excess of methyl iodide were employed, the *N,O*-dimethylated compound (VI) was isolated in low yield. The *N*-methylated ester III was subsequently prepared by an alternate synthetic route from monomethyl phthalate in an overall

yield of 70% (see Experimental section). This method, which does not require the isolation of intermediates, should be general for preparing any 2-substituted analogs of III provided the corresponding *N*-substituted glycine ester is available.

When thoroughly dry, the sodium salt of III was stable over prolonged periods while III itself slowly decomposed on standing.

Like the corresponding desmethyl analog I, the ester III proved to be extremely resistant to treatment with aniline. In a variety of solvents and at various temperatures only unreacted III or the decarboxylated form IV could be recovered. As an alternate approach to the desired 3-carboxanilides, IV was made by either acid or base catalyzed hydrolysis-decarboxylation of III. Compound IV was then treated with phenyl isocyanate in the presence of sodium hydride-dimethylformamide to give, presumably, the *O*-acylated derivative of IV. Thin-layer chromatographic evidence of the reaction indicated that IV had been completely converted to a new material. However, aqueous acidification of the mixture gave only recovered IV and 1,3-diphenylurea, presumably from hydrolysis of the *O*-acylated derivative of IV. Generally, *O*-alkylation of the enolate anion appears to be the favored reaction pathway for the ambient anion derived from IV as evidenced by the preparation of the *O*-alkyl compounds VI and VII (see Experimental section). Conditions were eventually developed for producing fair yields of the desired *C*-acylated products (the 3-carboxanilides V) from IV using sodium hydride and the appropriate aryl isocyanate in hexamethylphosphoramide as solvent. Under these conditions, some 1,3-disubstituted urea was isolated which again suggests some *O*-acylation of IV. Many of the carboxanilides V (Table I) formed tenacious hydrates or



hemihydrates which could not be dehydrated even at 110° under high vacuum. Infrared and nmr spectra support an enolic representation for V and the acidity of V, Ar = C₆H₅, in 2:1 dioxane-water was found to be 7.7.

The finding that IV was completely enolized in both the solid state (ir evidence) and in dimethylsulfoxide solution (nmr evidence) prompted a reinvestigation of the report of Caswell (3), which was based on ultra violet spectral evidence, that IIb exists in the 1,4-dione form. In our hands a sample of II, prepared by the method of Caswell (3), exhibited an infrared spectrum (potassium bromide) having no absorption below 6.0μ and broad OH-NH absorption near 3.4μ . A nmr spectrum of II in dimethylsulfoxide solution clearly showed an enolic OH near $\tau - 1.6$ and a single vinyl proton at $\tau 3.25$. Thus, both in the solid state and in dimethyl sulfoxide solution the enolic form IIa (4-hydroxyisocarbostyryl) appears to be

favored over the tautomeric keto form IIb ("1,2,3,4-tetrahydroisoquinoline-1,4-dione") (3). Similarly, infrared spectral data provide evidence for the enol ("4-hydroxy") structure for both esters I and III.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus in open capillaries and are uncorrected. A Varian A-60 spectrometer, using tetramethylsilane as an internal standard, was used to measure nmr spectra. Chemical shifts are reported in τ (s = singlet, d = doublet, t = triplet, m = multiplet). Ultraviolet spectra were measured on a Cary Spectrophotometer, Model 11. Infrared spectra were determined in potassium bromide pellets and mass spectra were measured on a Hitachi Perkin-Elmer Model RMU-6E. Analyses were carried out by the Physical Measurements Laboratory of Chas. Pfizer & Co., Inc.

Starting materials were commercially available and used as received except for 2,4-dichlorophenyl isocyanate which was made

TABLE I

4-Hydroxy-2-methylisocarbostyryl-3-carboxanilides (V)



Ar	Recrystn. Solvent	Yield %	M.p. °C	Formula	Calcd.		Analyses, %		Found	
					C	H	N	C	H	N
C ₆ H ₅	a	22	195-197	C ₁₇ H ₁₄ N ₂ O ₃ ·0.5H ₂ O	67.31	4.93	9.23	67.57	4.71	9.27
4-ClC ₆ H ₄	b	17	239-241	C ₁₇ H ₁₃ ClN ₂ O ₃ ·H ₂ O	58.88	4.36	8.08	59.03	3.99	7.97
2-CH ₃ OC ₆ H ₄	a	7	177-180	C ₁₈ H ₁₆ N ₂ O ₄ ·0.5H ₂ O	64.85	5.14	8.41	65.11	5.00	8.43
3-CF ₃ C ₆ H ₄	c	31	196-199	C ₁₈ H ₁₃ F ₃ N ₂ O ₃	59.67	3.62	7.73	59.48	3.68	7.72
3-ClC ₆ H ₄	d	28	228-230	C ₁₇ H ₁₃ ClN ₂ O ₃	62.10	3.98	8.52	61.89	3.95	8.43
2-ClC ₆ H ₄	d	31	210-212	C ₁₇ H ₁₃ ClN ₂ O ₃	62.10	3.97	8.54	61.88	3.99	8.37
4-CH ₃ OC ₆ H ₄	a	31	207-209	C ₁₈ H ₁₆ N ₂ O ₄	66.65	4.97	8.64	66.83	5.00	8.58
4-NO ₂ C ₆ H ₄	d	42	246 dec.	C ₁₇ H ₁₃ N ₃ O ₅ ·H ₂ O	57.14	3.95	11.76	57.42	3.81	11.88
3-CH ₃ C ₆ H ₄	a	47	208-209	C ₁₈ H ₁₆ N ₂ O ₃	70.10	5.20	9.10	69.88	5.11	8.96
2,4-diClC ₆ H ₃	b	27	233-234	C ₁₇ H ₁₂ Cl ₂ N ₂ O ₃ ·H ₂ O	53.56	3.70	7.35	53.37	3.56	7.34
2,5-diClC ₆ H ₃	d	7	228-230	C ₁₇ H ₁₂ Cl ₂ N ₂ O ₃	56.24	3.31	7.72	55.98	3.28	7.54

(a) 2-Propanol, (b) 1:1 Methanol-2-propanol, (c) Ether, (d) Methanol.

from phosgene and 2,4-dichloroaniline in toluene (10), m.p. 58-60° (reported (11) m.p. 57-58.8°).

4-Hydroxyisocarbostyryl-3-carboxylic Acid, Methyl Ester (I).

This compound was prepared by the procedure of Caswell and Atkinson (4); yield 72%, m.p. 219-220°; (reported (4) m.p. 222-223°). Infrared: 3.2, 3.3, 6.05 (shoulder), 6.1, 6.26, 7.41, 7.85 μ . Compound I gave a dark purple color with ferric chloride reagent.

4-Hydroxyisocarbostyryl (IIa).

Decarboxylation of I proceeded in 57% hydriodic acid under conditions described by Caswell and Campbell. A 77% yield of yellow powder was obtained, not melting below 300°, in agreement with previous reports (3,1). Ultraviolet spectrum: λ max (ethanol) 228 (shoulder), $\epsilon = 11,000$; 248, $\epsilon = 3,490$; 301, $\epsilon = 5,940$; 340, $\epsilon = 3,960$; λ max (0.1 N sodium hydroxide), 258, $\epsilon = 2,620$; 328, $\epsilon = 4,540$; 370, $\epsilon = 3,780$. (These values are in close agreement with those estimated from Figures 1 and 2 of reference 3). Infrared spectrum: 3.25-3.6 (broad), 6.1, 6.25, 12.96 μ ; nmr (deuteriodimethyl sulfoxide): τ 3.25 (s, 1-H, the 3-proton), 2.5-3.5 (broad, 1-H, exchanges deuterium oxide, the NH), 2.0-2.5 (m, 3-H, aromatic protons), 1.68 (d, 1-H, the 8-proton), -1.6 to 0 (broad, 1-H, exchanges deuterium oxide, the enol OH); mass spectrum: M^+ 161 (calcd. 161), also ions of m/e 144, 132, 105, 104, 78, 77, 76.

2-Methyl-4-hydroxyisocarbostyryl-3-carboxylic Acid, Methyl Ester (III).

A suspension of 14.6 g. (0.081 mole) of monomethyl phthalate and 11.8 g. (0.093 mole) of oxalyl chloride in 30 ml. of dry

benzene was warmed at 40° for 3 hours. The solution was then evaporated to dryness (reduced pressure), dry benzene added twice more, evaporating each time to a residual oil, which was dissolved in 100 ml. of dry chloroform at 0°, and treated with 11.8 g. (0.08 mole) of sarcosine methyl ester hydrochloride and then 24.5 g. (0.243 mole) of triethylamine. The resultant heavy suspension was refluxed for 1 hour, evaporated under reduced pressure, triturated thoroughly with benzene and filtered. Evaporation of the clear filtrate produced an oil which was dissolved in 75 ml. of refluxing methanol while 43.2 ml. of 2 M sodium methoxide in methanol was added over 5 minutes. The resulting yellow suspension was immediately cooled, filtered, washed with a little cold methanol, and dried to give 14.0 g. (70%) of the sodium salt of III which did not melt below 300°. This solid gave a very dark purple color with ferric chloride reagent.

The yellow sodium salt of III was dissolved in a minimum volume of water, acidified with 3 N hydrochloric acid to produce a white solid, III, m.p. 93-94°. Infrared: 6.04, 6.15, 6.26, 7.49, 8.03, 13.15 μ ; ultraviolet spectrum: λ max (ethanol), 226, $\epsilon = 16,300$; 245 (shoulder) and 256 (shoulder); 300, $\epsilon = 1,920$; nmr (deuteriochloroform): τ -1.34 (s, 1-H, exchanges deuterium oxide, enol OH), 1.5-2.5 (m, 4-H, aromatic protons), 6.0 (s, 3-H, ester OCH₃), 6.36 (s, 3-H, N-CH₃).

Anal. Calcd. for C₁₂H₁₁NO₄: C, 61.80; H, 4.76; N, 6.01. Found: C, 61.53; H, 4.61; N, 5.93.

2-Methyl-4-hydroxyisocarbostyryl (IV).

A suspension of 50.0 g. (0.19 mole) of the sodium salt of III in 1 liter of 3 N hydrochloric acid and 120 ml. of methanol was refluxed for 18 hours under a nitrogen atmosphere. Concentration of the resulting solution (by removal of the condenser) to 250 ml.,

followed by cooling, produced a heavy precipitate. Dilution with 400 ml. of water and filtration gave, in two crops, 27.2 g. (82%) of IV, m.p. 224-227°. Infrared: 3.25-3.75 (broad, enol OH), 6.09, 6.20, 6.40 μ ; ultraviolet spectrum: λ max (ethanol), 232, $\epsilon = 12,940$; 261, $\epsilon = 9,300$; 315, $\epsilon = 2,260$; nmr (deuterio-dimethyl sulfoxide): τ -0.84 (s, 1-H, exchanges deuterium oxide, enol OH), 1.74 (d, 1-H, the 8-proton), 2.0-2.6 (m, 3-H, aromatic protons), 3.10 (s, 1-H, the 3-proton), and 6.54 (s, 3-H, N-CH₃).

Anal. Calcd. for C₁₀H₉NO₂: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.28; H, 5.18; N, 7.99.

The identical product was obtained by refluxing the sodium salt of III in methanol with a slight excess over one equivalent of potassium hydroxide overnight. On evaporation of all solvent and acidification (3 N hydrochloric acid), IV was obtained in 57% yield, m.p. 222-224°.

3'-Chloro-4-hydroxy-2-methylisocarbostyryl-3-carboxanilide.

All of the carboxanilides in Table I were prepared from IV and an isocyanate by essentially the same procedure. The following experiment illustrates the general method:

A 50% suspension of sodium hydride in mineral oil (0.82 g., 0.017 mole) was triturated with dry hexane and the hexane carefully decanted. To the residual gray powder was added 25 ml. of hexamethylphosphoramide (HMP). While stirring, a small portion (ca. 10%) of a solution of 2.6 g. (0.015 mole) of IV in 10 ml. HMP was added followed by a portion (ca. 10%) of a solution of 2.6 g. (0.017 mole) of *m*-chlorophenyl isocyanate in 10 ml. of HMP. This alternating mode of addition was continued over 25 minutes after which the dark suspension was stirred at room temperature for 90 minutes. Pouring the reaction in a fine stream into 200 ml. of water containing 10 ml. of 6 N hydrochloric acid gave a white solid which was collected. This solid was partially dissolved in 100 ml. of 1% sodium hydroxide and filtered. Acidification of the clear filtrate produced a gel-like material which was filtered and dried (under vacuum over phosphorus pentoxide) to give, after recrystallization from 2-propanol, 1.1 g. (28%) of 3'-chloro-4-hydroxy-2-methylisocarbostyryl-3-carboxanilide, m.p. 228-230°.

See Table I for analytical data. Infrared: 3.01, 3.2-3.4 (broad), 5.98, 6.11, 6.27, 6.35, 6.50, 13.02 μ ; nmr (deuteriodimethyl sulfoxide): τ -1.06 (broad, 1-H, exchanges deuterium oxide, the enol OH), 0.80 (broad, 1-H, exchanges deuterium oxide, the NH), 1.46 (d, 1-H, the 8-proton), 1.8-2.9 (m, 7-H, aromatic protons), 6.58 (s, 3-H, N-CH₃). This compound (and all other 3-carboxanilides in this series) gave a deep purple color with ferric chloride reagent.

4-Methoxy-2-methylisocarbostyryl-3-carboxylic Acid, Methyl Ester (VI).

A suspension of 50% sodium hydride in mineral oil (0.51 g., 0.0105 mole) was triturated with dry hexane and the hexane carefully decanted. To the gray residue was added a solution of 1.1 g. (0.005 mole) of I in 75 ml. of dry dimethylformamide. After

stirring for 15 minutes, a solution of 6.0 g. (0.042 mole) of methyl iodide in 5 ml. of dimethylformamide was slowly added. After stirring for 30 minutes, warming for 45 minutes (50°) gave a clear yellow solution. After pouring into an excess of 3 N hydrochloric acid, the suspension was extracted exhaustively with ether and the extracts dried (calcium sulfate). Evaporation and recrystallization from ethanol-water gave 0.324 g. (27%) of VI, m.p. 127-129°. A sample failed to give any color with ferric chloride reagent. Infrared: 5.76, 6.01, 7.76, 8.0 μ ; nmr (deuteriochloroform): τ 1.56 (d, 1-H, the 8-proton), 2.10-2.8 (m, 3-H, aromatic protons), 6.04 (s, 3-H, ester OCH₃), 6.18 (s, 3-H, N-CH₃), 6.56 (s, 3-H, vinyl ether OCH₃).

Anal. Calcd. for C₁₃H₁₃NO₄: C, 63.15; H, 5.40; N, 5.67. Found: C, 62.95; H, 5.51; N, 5.67.

4-Benzyloxy-2-methylisocarbostyryl-3-carboxylic Acid, Methyl Ester (VII).

To 2.6 g. (0.010 mole) of the sodium salt of III in 25 ml. of dimethyl formamide was added 2.01 g. (0.012 mole) of α -bromotoluene. After stirring for 15 minutes at room temperature and for 25 minutes at 100°, the reaction was poured into 200 ml. of water, extracted twice with ether and the ether extracts dried (calcium sulfate). Evaporation and recrystallization of the residue from ether gave, in two crops, 0.50 g. (16%) of VII, m.p. 144-146°. This material gave no coloration with ferric chloride reagent. Infrared: 5.76, 6.02, 6.15, 6.24, 7.55, 7.81, 8.04, 13.20, 14.26 μ .

Anal. Calcd. for C₁₉H₁₇NO₄: C, 70.57; H, 5.30; N, 4.33. Found: C, 70.42; H, 5.29; N, 4.23.

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