A Process Synthesis of the Disubstituted Amsacrine Analog CI-921

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An improved process for the synthesis of bulk quantities of the clinical amsacrine analog CI-921 is reported. Described also are detailed analytical and spectroscopic data for this agent.

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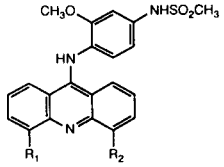
Introduction.

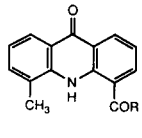
Amsacrine (**1**), an anilinoacridine analog synthesized in 1974 by Cain and Atwell [1], has been extensively studied in both leukemias and solid tumors. Worldwide clinical trials have demonstrated that its major utility is in the chemotherapy of acute leukemias. It also possesses limited activity against lymphomas, but in most human solid tumors the overall response rate to amsacrine has been quite low [2,3].

Attempts to develop analogs of amsacrine with superior activity against solid tumors has resulted in a large series of anilinoacridine compounds [4]. These agents were tested biologically by examining activity against a number of solid tumor lines *in vitro* and *in vivo* as well as against leukemias. From these studies a 4,5-disubstituted compound, 9-[{2-methoxy-4-[(methylsulfonyl)amino]phenyl}-amino]-*N*,5-dimethyl-4-acridinecarboxamide (**2**), designated as CI-921, was selected for clinical development because of its experimental activity against both solid tumors and leukemias [5,6]. A Phase 1 human trial of this compound has recently been reported [7], and Phase 2 trials are now in progess.

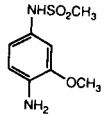
Denny *et al.* have briefly described the synthesis of CI-921 *via* the *in situ* elaboration and coupling of the intermediate 5-methylacridone-4-carboxylic acid (**3**) with *N*-(4-amino-3-methoxyphenyl)methanesulfonamide (**5**) [6]. In this paper we describe fully the large-scale synthesis of CI-921, incorporating improvements into one of their earlier sequences, and provide detailed analytical and spectral data for this agent and several synthetic intermediates.



1: $R_1 = R_2 = H$ (Amsacrine)
2: $R_1 = CH_3$; $R_2 = CONHCH_3$ (CI-921)



3: R = OH
4: R = $NHCH_3$



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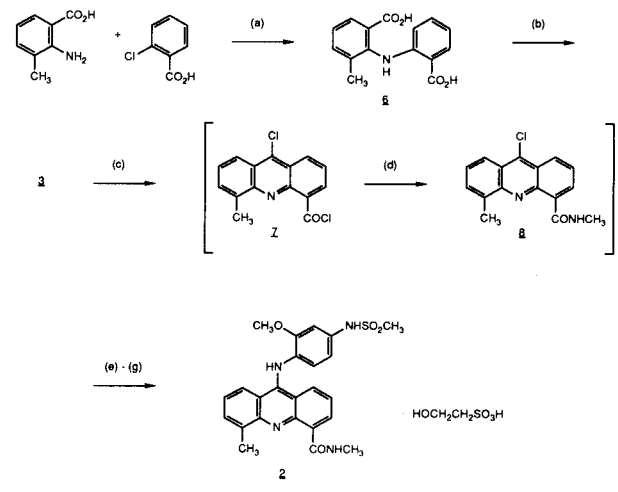
Results and Discussion.

The process synthesis of CI-921 (**2**) is outlined in Scheme 1. Ullman-type reaction of the commercially available 2-amino-3-methylbenzoic acid and 2-chlorobenzoic acid in *N*-methyl-2-pyrrolidinone at 160° gave a 98% yield of the coupled anthranilic acid **6**. Ring closure of **6** in concentrated sulfuric acid proceeded smoothly to give the key acridone carboxylic acid intermediate **3** in 86% yield. Conversion of **3** to CI-921 *via* the intermediacy of **7** and **8**

Scheme 1

Synthesis of Amsacrine Analog CI-921 (2)



Reagents: (a) K_2CO_3, Cu, CuBr, NMP (b) Conc. H_2SO_4 (c) $SOCl_2$, DMF (d) 40% aq CH_3NH_2, $CHCl_3$ (e) Anilin

5, conc. HCl, $CHCl_3$:NMP (3:2) (f) $(2\text{-Pr})_2NEt$, DMF (g) methanolic $HOCH_2CH_2SO_3H$, DMF

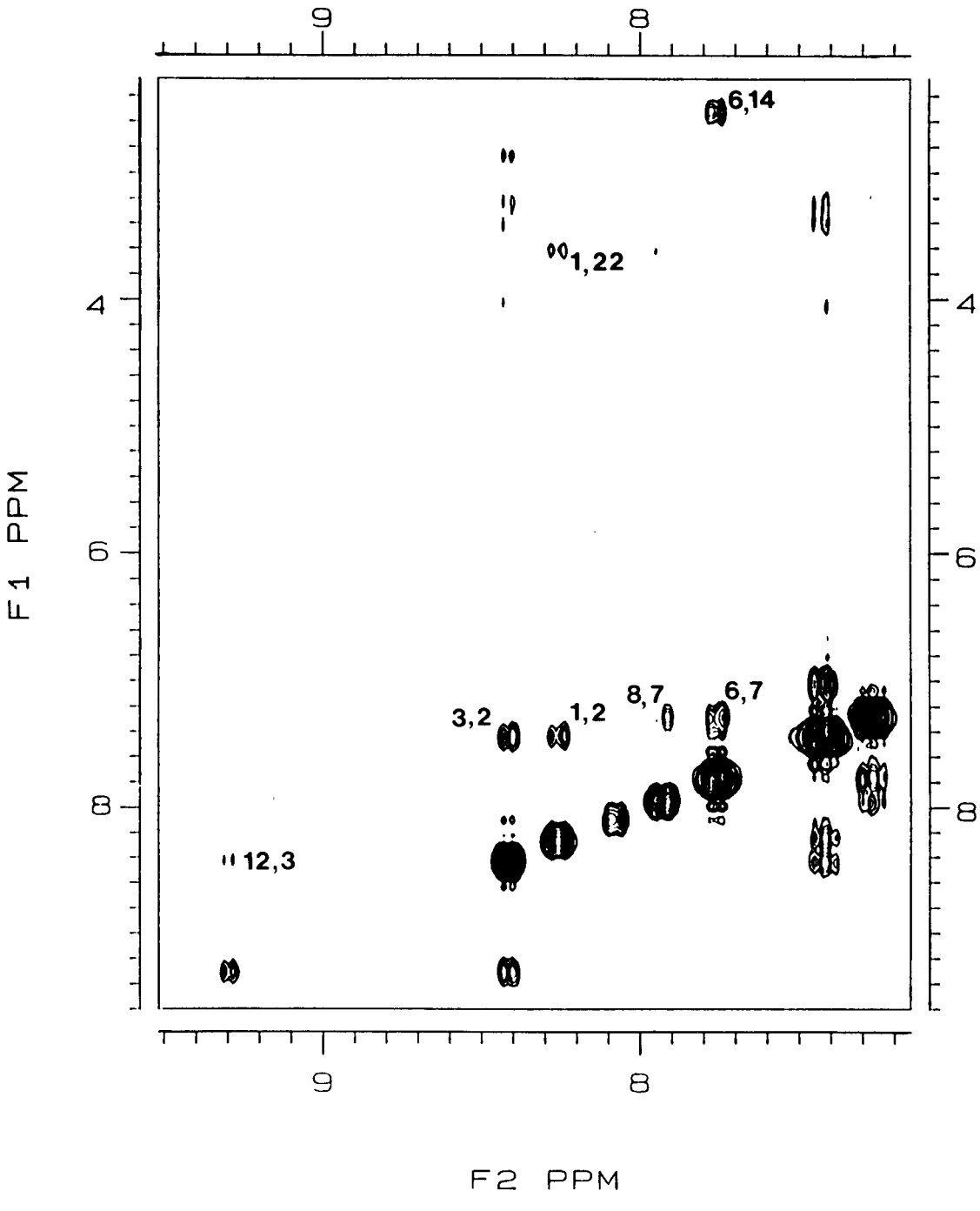


Figure 1. Contour plot of the NOESY spectrum of CI-921 in DMSO-d_6 at 25°. Crosspeaks crucial to distinguishing the C-1, C-2 and C-3 protons from the C-6, C-7 and C-8 protons are labeled. See Experimental text for spectral parameters.

was carried out in a one-pot series of reactions. Chlorination of **3** with thionyl chloride followed by selective displacement reactions first with aqueous methylamine then with *N*-(4-amino-3-methoxyphenyl)methanesulfonamide (**5**) gave the hydrochloride salt of CI-921 in 99% yield. In the first displacement step, it was essential that the aqueous methylamine be added as a single charge. Experiments in which the methylamine was added dropwise to the acid chloride **7** resulted in drastic reductions in yield to **8** due to the competing hydrolysis of **7** to the acid **3**.

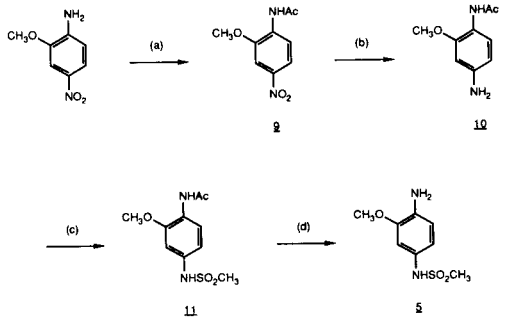
In formulation studies with CI-921, we evaluated a number of salt forms and determined that the isethionic acid salt gave optimal solubility characterisitics in aqueous vehicles. Conversion of CI-921 to high purity isethionate salt was carried out in 74% yield by digestion of the hydrochloride salt in a mixture of *N,N*-diisopropylethylamine and *N,N*-dimethylformamide to give the free base, followed by salt formation in methanol. Solutions of the isethionic acid salt were found to be stable in sterile water and 5% dextrose over a one day period. The overall yield of CI-921 isethionate utilizing the chemistry shown in Scheme 1 was 62%.

We have evaluated various bulk lots of CI-921 by high performance tlc and hplc for the presence of potential impurities derived from incomplete reaction of precursor compounds **3** and **5**, or from the hydrolysis of intermediate **8** to give carboxamide **4**. In some lots, anilino compound **5** and/or acridone carboxamide **4** were present at very low levels, usually 0.1-0.5%. The development of chromatographic systems, which completely resolve CI-921 from these potential impurities, is given in the Experimental Section.

The process synthesis of *N*-(4-amino-3-methoxyphenyl)-methanesulfonamide (**5**), the anilino moiety of CI-921, is shown in Scheme 2 and parallels closely the sequence previously reported [8] but uses the more crystalline acetamide intermediates. Briefly, acetylation of commercially available 2-methoxy-4-nitroaniline gave the crystalline acetamide **9** [9] in 97% yield. Nitro reduction *via* Raney nickel or palladium on carbon catalyzed hydrogenation gave the air-sensitive aniline **10** which was directly converted to the sulfonamide **11** in 90% overall yield from **9**. A similar two-step conversion of acetamide **9** to sulfonamide **11** was reported recently by Sundberg *et al.* [10]. Acetamide hydrolysis of **11** gave the target sulfonamide **5** [8] in 82% yield. The overall yield of **5** *via* this sequence of reactions was 72%.

Scheme 2

Synthesis of N-(4-Amino-3-methoxyphenyl)methanesulfonamide (5)



Reagents: (a) Ac_2O, HOAc (b) 5% Pd/C, H_2, CH_3OH (c) CH_3SO_2Cl, pyridine, CH_2Cl_2 (d) HCl, aq. EtOH, then conc. NH_4OH

The specific proton and carbon nmr assignments for CI-921 are given in Table I. Initial proton assignments were made on the basis of splitting patterns and chemical shift. In cases where similar magnetic environments precluded unambiguous assignments, two dimensional nuclear Overhauser spectroscopy (NOESY) was used to qualitatively identify which protons were close in space. The 250 MHz NOESY spectrum of CI-921 is shown in Figure 1 with important crosspeaks labeled. With the proton assignments distinguished, all the protonated carbon assignments were forthcoming from a standard INEPT-type heteronuclear correlation (HETCOR) experiment [11] with the final delay optimized for $^1J_{C\text{-}H}$ of 140 Hz. The nonprotonated carbons were subsequently assigned based on their distantly bound protons using the HETCOR pulse sequence with the final delay optimized for an 11 Hz ^{13}C-^1H coupling (LR-HETCOR). To verify these difficult carbon assignments, a heteronuclear correlation with fixed evolution time (XCORFE) [12] was also performed. The 75 MHz XCORFE spectrum is shown in Figure 2 with each of the crosspeaks labeled to identify the ^{13}C- $(^{12}C)_n$-^1H coupling from whence it arises. Note also that the multiple correlations provided by the LR-HETCOR and the XCORFE experiments have the added benefit of providing redundant (overlapping) information and hence confirming assignments made by other means.

In summary, we have detailed an improved process for the synthesis of bulk quantities of the amsacrine analog clinical agent CI-921. We have also provided detailed analytical and spectroscopic data for this agent and some of the intermediates and impurities of its synthesis.

EXPERIMENTAL

Melting points (mp) were taken on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Infrared (ir) spectra were determined on a Digilab FTS-14 or Nicolet MX-1 FT-IR spectrometer system. Ultraviolet (uv) spectra were taken on a Cary Model 118C recording spectrophotometer. Routine proton magnetic resonance (pmr) spectra were recorded on a Varian EM-390 or XL-200 spectrometer operating at 90 MHz or 200 MHz, respectively. Two dimensionl nmr correlation spectra

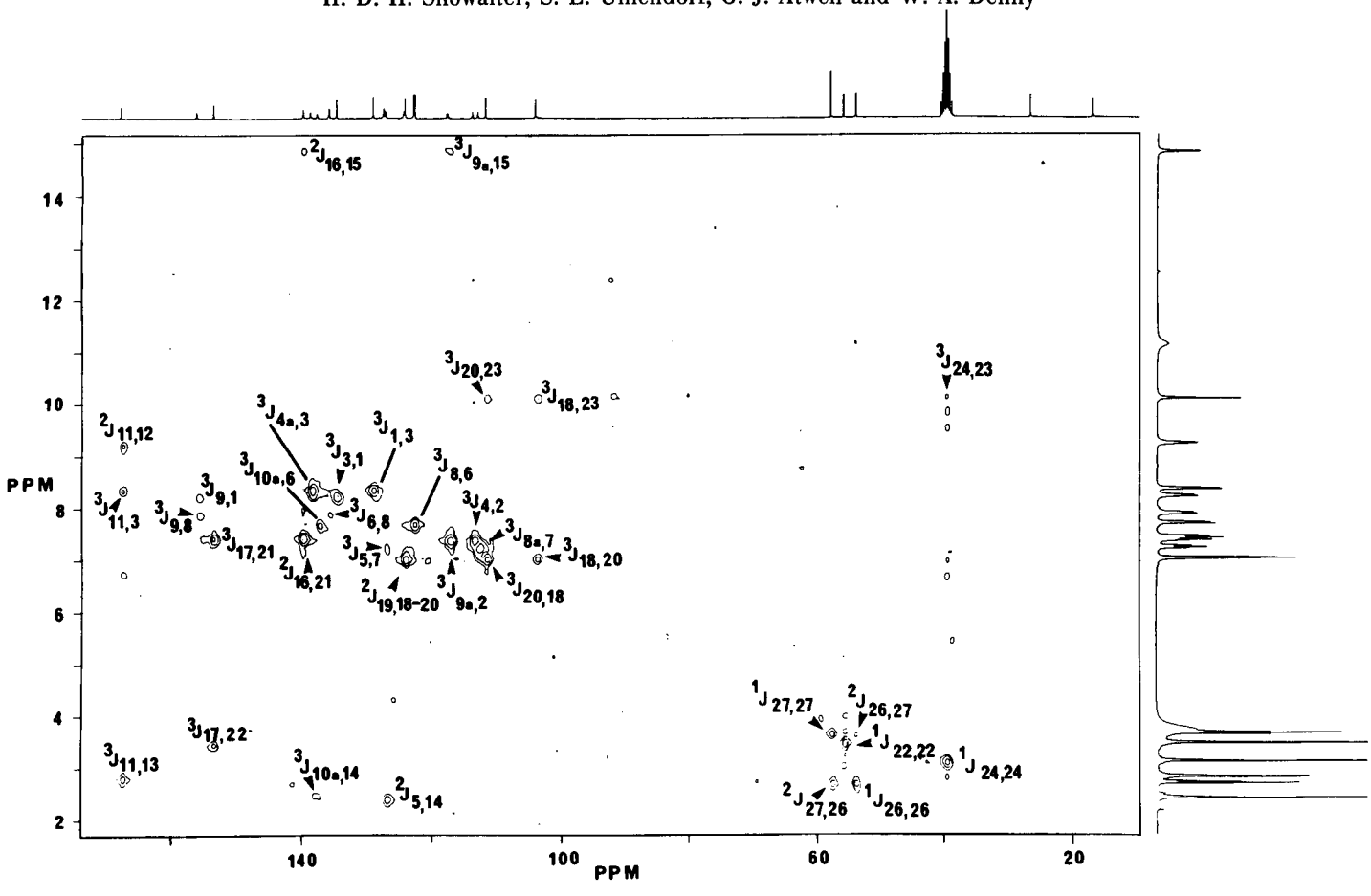


Figure 2. Contour plot of the entire ^{13}C-^1H XCORFE spectrum of CI-921 in DMSO-d_6 at 25°. The one dimensional proton and carbon spectra are plotted on the vertical and horizontal, respectively. The cross peaks correlate protons and carbon-13 nuclei that are 2-3 bonds apart. The labels have the format $^lJ_{m,n}$, where l is the number of bonds between the proton and the ^{13}C nucleus and m and n are the numbers of the coupled carbon and proton nuclei, respectively. Protons 18 and 20 are coincident and as a result, a single correlation is observed corresponding to $^2J_{19,20}$ and $^2J_{19,18}$. These data provide the basis for assigning nonprotonated carbons and corroborate previous proton and carbon assignments (see text). See Experimental for spectral parameters.

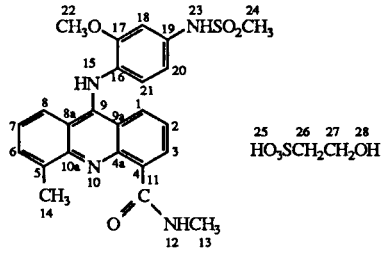
were recorded on a Varian XL300 equipped with a Varian broadband switchable probe with the observe coil tuned for ^{13}C and the decoupler coil tuned for protons. The ^{13}C-^1H correlation (HETCOR) spectra were obtained in the absolute value mode by acquiring 128 blocks of 2048 complex data points over a ^{13}C sweep width of 11-145 ppm. A total recycle time of 1.1 seconds was used between pulses and 48 scans were averaged for each block. Prior to the first Fourier transformation, a signal enhancement function was applied to the t_2 (carbon) fids (SE = 3.18 and AF = 0.061). A similar function was applied to the resulting t_1 (proton) interferograms (SE = 3.18 and AF = 0.034) before the second Fourier transformation. The long range ^{13}C-^1H correlation (LR-HETCOR and XCORFE) spectra were obtained similarly, except that the entire ^{13}C chemical shift range was excited and 256 blocks of 256 transients each were recorded. The final delays in the LR-HETCOR were set to optimize for J_{CH} = 11 Hz. The XCORFE experiment was recorded using a fixed evolution time of 3.17 ms and a 50 ms refocusing delay was used before and after the final BIRD pulse. Also, similar filters were applied to the t_2 fids (SE = 3.18 and AF = 0.050) and the t_1 interferograms (SE = 3.18 and AF = 0.037) before their respective Fourier transformations. The NOESY experiments were performed on a Bruker AM250 spectrometer in absolute value mode by recording 256 blocks of 1024 complex data points over the entire ^1H spectrum. A total of 16 transients were averaged for each block. The mixing time was randomly varied between 0.98 and 1.02 sec to reduce crosspeaks from scalar coupling. The total time between each pulse was 2.1 sec. A sine bell was applied to both t_2 fids and t_1 interferograms prior to Fourier transformation. Chemical shifts are reported as δ units in parts per million downfield from internal tetramethylsilane.

Combustion analyses were performed on a Perkin-Elmer Model 240, Control Equipment Corporation Model 240XA, or Carlo-Erba Model 1106 elemental analyzer. Water of crystallization was determined by Karl Fischer titration.

Chromatography was carried out with (a) E. Merck products

Table I

NMR Chemical Shift Assignments (δ) for CI-921 Isethionate (2) [a]



Position	^{1}H	^{13}C (Number of Attached Protons)	Position	^{1}H	^{13}C (Number of Attached Protons)
1	8.30	128.9 (1)	14	2.54	16.7 (3)
2	7.36	127.3 (1)	15	14.9	
3	8.45	134.6 (1)	16		139.8 (0)
4		113.9 (0)	17		153.6 (0)
4 a		138.7 (0)	18	7.03 [b]	104.1 (1)
5		127.0 (0)	19		124.2 (0)
6	7.80	135.8 (1)	20	7.03 [b]	111.9 (1)
7	7.31	123.9 (1)	21	7.46	122.4 (1)
8	7.98	122.6 (1)	22	3.51	55.7 (3)
8 a		113.1 (0)	23	10.1	
9		156.2 (0)	24	3.14	39.5 (3)
9 a		117.6 (0)	25	11.2	
10 a		137.7 (0)	26	2.68	53.7 (2)
11		167.8 (0)	27	3.66	57.8 (2)
12	9.33		28	[c]	
13	2.89	26.5 (3)			

[a] Spectra obtained in d_6-dimethyl sulfoxide. [b] H-18 and H-20 are overlapping multiplets. [c] Signal not observed and assumed to overlap with water signal at 3.63.

utilizing silica gel 60, catalog No. 5789, for normal phase tlc. Solvents utilized included A: ethyl acetate; B: ethyl acetate:ethanol (4:1); (b) Analtech C-18 silica gel, catalog No. 52031, for reverse-phase tlc with development in acetonitrile:water: 0.25 *M* aqueous dipotassium hydrogen phosphate (8:11:1), (c) E. Merck silica gel 60, catalog No. 5628 for high performance tlc (hptlc). Plates were predeveloped with methanol and dried. Samples of compound **2** (CI-921) were dissolved in chloroform:methanol (7:3) at 1.0 mg/ml and compounds **3**, **4** and **5** in chloroform at 0.005 mg/ml. Ten-microliter aliquots of CI-921 or 50 ng each of the other test agents was applied as a 5 mm band with a Camag Linomat III device. A Camag Linear developing chamber was utilized, and the plate was developed to a distance of 6.5 cm with a mixture of chloroform:acetone:methanol (75:20:5). The plate was then dried and scanned with a Camag TLC Scanner Model 76511 densitometer at 254 nm with a 10 nm band width. A Spectra-Physics Model 4100 integrator was used for display of the densitogram and for computation of peak areas.

High pressure liquid chromatography (hplc) was carried out on an Altex, C-18, 5 μm column (or equivalent). The mobile phase was a mixture composed of 40 parts of acetonitrile and 60 parts of an aqueous buffer prepared in the following manner: 0.02 mole of disodium hydrogen phosphate and 0.001 mole of 1-octanesulfonic acid sodium salt was diluted in water to 1 liter. Ten ml of glacial acetic acid was added to this solution which was then adjusted to *p*H 3 with phosphoric acid. The flow rate was 1.5 ml/minute and peaks were monitored at 254 nm. Test samples were made up at 0.2 mg/ml in the mobile phase and applied as 20 ul injections. This system completely resolves CI-921 (**2**) from potential synthetic impurities **3**, **4** and **5**.

All solvents and reagents utilized in reactions were "reagent grade." Solvents were predried over activated 4A molecular sieves. Charcoal clarification was carried out with "Darco G-60".

2-[(2-Carboxyphenyl)amino]-3-methylbenzoic Acid (**6**).

A 5 liter round bottom flask equipped with a mechanical stirrer, thermometer, and a nitrogen inlet tube was charged with a mixture of 336.5 g (2.226 moles) of 2-amino-3-methylbenzoic acid, 380 g (2.43 moles) of 2-chlorobenzoic acid, and 1 liter of *N*-methyl-2-pyrrolidinone. To the stirred slurry was added 733 g (5.3 moles) of anhydrous potassium carbonate, 4 g of copper(I) bromide, and 8 g of activated copper powder [13]. The suspension was brought to 160° over 35 minutes and maintained there for 30 minutes. After brief cooling, the hot slurry was poured into 16 liters of water, and the resultant mixture was decolorized with 140 g of charcoal. The stirred dark filtrate was acidified with 1.2 liters of acetic acid and the formed precipitate was collected by filtration. The solids were suspended in 10 liters of water at 70°

with vigorous stirring, then collected by filtration. The wet filter cake was dissolved in a solution of 6 liters of 5% aqueous sodium carbonate and the solution was treated with 100 g of charcoal. The clarified solution was heated to boiling on a steam bath, diluted with 6 liters of 3A ethanol, and acidified by the slow addition of 400 ml of acetic acid. The hot solutiion was refrigerated for three days and the precipitated diacid was collected by filtration. The solids were air dried for 24 hours, then dried at 250 mm/90°/6 hours to give 422 g (70%) of **6** as an off-white solid.

The filtrate was diluted to 19 liters with water, the solution refrigerated overnight, and the precipitated solids were collected and dried as above to give 169 g of additional product; total yield = 591 g (98%).

Both crops were suitable for ring closure to **3**. Crystallization of a small sample from ethanol:water provided analytically pure product as colorless needles, mp 258-259°; ir (potassium bromide): 1675, 1588, 1576, 1509, 1453, 1265, 1163 cm^{-1}; pmr (d_6-dimethyl sulfoxide): δ 2.10 (s, 3H), 6.14 (d, J = 7 Hz, 1H), 6.68 (t, J = 7 Hz, 1H), 7.05-7.90 (m, 5H), 9.80 (br s, 1H, exchanges deuterium oxide), 12.73 (br s, 1H), exchanges deuterium oxide).

Anal. Calcd. for $C_{15}H_{13}NO_4 \cdot 0.1\ H_2O$: C, 65.98; H, 4.87; N, 5.13. Found: C, 65.95; H, 4.83; N, 4.96.

9,10-Dihydro-5-methyl-9-oxo-4-acridinecarboxylic Acid (**3**).

A three liter round bottom flask equipped with a mechanical stirrer and a thermometer was charged with 1.5 liters of concentrated sulfuric acid. Dicarboxylic acid **6** (590 g, 2.175 moles) was added portionwise over *ca.* 30 minutes, and the resulting slurry was brought to 90° where it was maintained for two hours. The solution was cooled to 25° overnight and poured into 30 liters of water. The precipitated solid was collected by filtration, and the filter cake was washed with warm (50°) water, and 400 ml of ammonium hydroxide, then filtered. The stirred filtrate at 75° was acidified with 880 ml of acetic acid and the resultant slurry was maintained at 75° for *ca.* 45 minutes. The slurry was cooled to *ca.* 10°, and the bright yellow precipitate was collected by filtration, then washed successively with 3.7 liter portions each of water and acetone. The solids were dried first at 60°/250 mm/two days, then at 100°/5 mm/one hour to give 475.4 g (86%) of analytically pure **3** as bright yellow prismatic crystals, mp 358-362°; tlc (system aB), R_f = 0.21; hptlc (system c), R_f = 0.09; ir (potassium bromide): 1683, 1622, 1597, 1570, 1530, 1440, 1240, 1180, 1145, 750 cm^{-1}; pmr (d_6-dimethyl sulfoxide): δ 2.50 (s, 3H), 7.03-7.40 (m, 2H), 7.58 (d, 6 Hz, 1H), 8.02 (d, 8 Hz, 1H), 8.23-8.50 (m, 2H), 12.0 (s, 1H, exchanges deuterium oxide).

Anal. Calcd. for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 70.67; H, 4.53; N, 5.46.

9-[[2-Methoxy-4-[(methylsulfonyl)amino]phenyl]amino]-*N*,5-dimethyl-4-acridinecarboxamide, Isethionic Acid Salt (**2**).

A 3 liter round bottom flask equipped with an efficient condensor connected to a gas scrubber was charged with 63.3 g (250 mmoles) of acridone **3**, 337 ml (4.62 moles) of thionyl chloride and 0.4 ml of anhydrous *N,N*-dimethylformamide. The mixture was heated at reflux until solution resulted (*ca.* 10 minutes) and then for 30 minutes more. The solution was concentrated *in vacuo* to a residue that was co-evaporated with anhydrous *p*-dioxane (3 x 500 ml). The bright yellow solid **6** was diluted with 1.2 liters of ethanol-free chloroform, prepared by passage over activity grade 1 alumina. To the vigorously stirred 0° suspension was added in one charge 99 ml (1.18 moles) of 40% w/v aqueous methylamine precooled to 0°. There was an initial and brief exotherm to *ca.* 20° and the suspension changed from a transient black to yellow color with complete solution occuring after *ca.* 15 minutes. The solution was stirred vigorously at 0° for 30 minutes, then diluted with 400 ml of water. The chloroform layer of chloroacridine **8** was separated, washed successively with water (8 x 400 ml) and 300 ml of brine, dried, and filtered.

To the chloroform solution of **8** at 25° was added 57.3 g (265 mmoles) of *N*-(4-amino-3-methoxyphenyl)methanesulfonamide (**5**), predissolved in 785 ml of anhydrous *N*-methyl-2-pyrrolidinone, followed by 0.8 ml of concentration hydrochloric acid. The mixture was stirred at reflux for 30 minutes, then 800 ml of solvent was distilled off at 760 mm. The hot suspension was diluted with 800 ml of hot ethyl acetate, then cooled at 5° for two days. The deep orange solid was collected by filtration, washed with ethyl acetate, and air dried to give 124 g (99%) of the hydrochloride salt of **2**, mp 290-292° dec.

High-purity free base of **2** was generated as follows: A suspension of 1.638 kg (3.269 moles) of the hydrochloride salt of **2** in one liter of diisopropylethylamine and six liters of *N,N*-dimethylformamide was stirred vigorously at 75° for 12 hours. The mixture was cooled to 25° overnight and filtered. The filter cake was washed successively with *ca.* 1.36 liters of *N,N*-dimethylformamide, *ca.* 13.5 liters of water, and *ca.* two liters of methanol. The solids were air dried overnight, then at 70°/5 mm over phosphorus pentoxide for one day to leave 1.263 kg (83%) of analytically pure free base of **2** as a bright orange powder; mp 282-284° dec, 99.9% pure by hplc; solubility = 5.8 mg/ml (*N,N*-dimethylformamide), 15.7 mg/ml (*N,N*-dimethylacetamide).

The isethionate salt of **2** was generated as follows: To a vigorously stirred suspension of 179 g (385 mmoles) of the purified base of **2** and 530 ml *N,N*-dimethylformamide maintained at 45° was added 405 mmoles of a methanolic solution of isethionic acid dihydrate (1.05 *M*). After 10 minutes the warm solution was diluted with 260 ml of 1:1 ethyl acetate:hexanes. The mixture was kept at 5° for 3.5 hours. The precipitated salt was filtered, washed well with ethyl acetate, and air-dried overnight to leave the isethionate salt of **2** as a deep orange solid, mp 265-267° (lit [6] mp 254-256°). A stirred suspension of the solid in 1.6 liters of 1:1 methanol:water was heated at 65° until complete solution resulted. The solution was filtered hot, diluted with 3 liters of methanol, then maintained at 5° for three days. The precipitated solids were filtered, washed well with 2-propanol, then ethyl acetate, and dried at 200 mm/65°/two days over phosphorus pentoxide to leave 138 g of the pure isethionate salt of **2** as a bright orange solid, mp >146° dec, 100% pure by hplc.

The mother liquor was concentrated to near dryness. The solids were dissolved in 1.3 liters of hot methanol:water (85:15), and the solution was diluted with 600 ml of 2-propanol. The solution was maintained at 5° for two days and the precipitated solids were recovered as above to leave 72 g of additional pure product; mp >146° dec, 100% pure by hplc; total recovery 210 g (90%); tlc (system b), R_f = 0.25; hptlc (system c), R_f = 0.46; pKa (50% methanol) = 6.5; solubility = 7.5 mg/ml (water, solution *p*H = 3.9); ir (potassium bromide): 1610, 1578, 1515, 1445, 1325, 1200, 1155, 1030 cm^{-1}; uv (methanol): λ 253 nm (ε = 46930), 440 (11360).

Anal. Calcd. for $C_{24}H_{24}N_4SO_4 \cdot C_2H_6SO_4 \cdot H_2O$: C, 51.30; H, 5.31; N,

9.21; S, 10.53. Found: C, 51.20; H, 4.93; N, 9.11; S, 10.53.

Preparation of Isethionic Acid Dihydrate.

A suspension of 74 g (0.5 mole) of isethionic acid, sodium salt, was dissolved in 25 ml of water. The solution was treated with 63 ml of concentrated hydrochloric acid, heated on a stream bath for 30 minutes, then diluted with 750 ml of acetone. After standing at 5° overnight, precipitated sodium chloride was filtered off and washed well with dry acetone. The filtrate was evaporated to a viscous oil that was co-evaporated with methanol (3 x 200 ml), then layered with acetone. Upon standing at 5° overnight, a small amount of additional sodium chloride precipitated. This was filtered off and the filtrate was concentrated to an oil that was dissolved in methanol. The solution was decolorized with charcoal, then concentrated to an oil that was evacuated at 1 mm/25°/three days to leave 56 g (70%) of isethionic acid dihydrate as a chloride-free oil. The oil was dissolved in 250 ml of methanol and the solution was titrated with 0.1 *N* aqueous sodium hydroxide. The methanolic solution is indefinitely stable when stored at 0-5°.

Alternatively, a solution of 0.5 kg (3.378 moles) of isethionic acid, sodium salt, in two liters of methanol was treated with 1.2 liters of Amberlite IR-120 prewashed in methanol. The mixture was stirred at room temperature for one hour and filtered. The filtrate was subjected to a second treatment cycle with 0.6 liter of the resin. The combined resin residues were washed with one liter of methanol. The washings and filtrates were combined, titrated as above, and adjusted to 1*N* with methanol to yield 3 moles (89%) of 1*N* isethionic acid solution.

9,10-Dihydro-*N*,5-dimethyl-9-oxo-4-acridinecarboxamide (**4**).

A dried chloroform solution of intermediate chloroacridine **8**, used in the synthesis of CI-921 (**2**), was concentrated to dryness to leave a crude solid. A sample (2.0 g, 6.9 mmoles) was finely powdered and suspended in 100 ml of warm 95% ethanol. Concentrated hydrochloric acid (2 ml) was added, and the suspension was heated until it became homogeneous and then kept at 20° for 6 hours. The resulting microcrystals were collected and washed well with 50% aqueous ethanol to give 1.8 g (95%) of analytically pure **4**, mp >310°; hptlc (system c), R_f = 0.64; ir (potassium bromide): 3367, 1617, 1580, 1530, 1438, 1312 cm^{-1}; pmr (d_6-dimethyl sulfoxide:deuterium oxide, *ca.* 20:1): δ 2.55 (s, 3H), 2.90, 2.92 (s each, 3H), 7.24 (t, J = 7.6 Hz, 1H), 7.37 (t, J = 7.8 Hz, 1H), 7.67 (d, J = 71. Hz, 1H), 8.11 (d, J = 8.2 Hz, 1H), 8.31 (d, J = 7.7 Hz, 1H), 8.44 (d, J = 8.0 Hz, 1H).

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.41; H, 5.13; N, 10.50.

N-(2-Methoxy-4-nitrophenyl)acetamide (**9**).

A three liter flask was charged with 250 g (1.487 moles) of 2-methoxy-4-nitroaniline and 1.4 liters of glacial acetic acid followed by 155 ml (1.636 moles) of acetic anhydride resulting in a 3° exotherm. The stirred mixture was heated to 80° (solution formed at *ca.* 45°), then stirred without additional heating for one hour. The slurry was cooled to *ca.* 5° and filtered. The solids were washed with water (3 x 1.5 liters) and dried (10°/250 mm/18 hours) to give 304 g (97%) of analytically pure acetamide **9** as a light tan crystalline solid, mp 155-156° (lit [9] mp 153.5-154.5°); tlc (system aA), R_f = 0.66; ir (potassium bromide): 1676, 1592, 1552, 1510, 1339, 1284, 1097, 1028 cm^{-1}; pmr (deuteriochloroform): δ 2.27 (s, 3H), 4.01 (s, 3H), 7.75 (d, J = 2.4 Hz, 1H), 7.92 (dd, J = 9.0, 2.4 Hz, 1H), 7.97 (br s, 1H, exchanges deuterium oxide), 8.58 (d, J = 9.0 Hz, 1H).

Anal. Calcd. for $C_9H_{10}N_2O_4$: C, 51.43; H, 4.80; N, 13.33. Found: C, 51.54; H, 4.41; N, 13.34.

N-(4-Amino-2-methoxyphenyl)acetamide (**10**).

A mixture of 597 g (2.84 moles) of *N*-(2-methoxy-4-nitrophenyl)-acetamide (**8**), 25 g of Raney nickel, and 4.5 liters of methanol was hydrogenated at 50 psi in a two-gallon stirred autoclave. After 22.5 hours the theoretical amount of hydrogen had been consumed and the mixture was filtered. This procedure was repeated for a 592 g (2.816 moles) lot of acetamide **9**. The combined filtrates were concentrated to a viscous oil that was dissolved in 10 liters of dichloromethane. The air-sensitive solution of **10** was dried (magnesium sulfate) and filtered while being maintained under nitrogen, then used directly in the next step.

This reduction can also be carried out in nearly quantitative yield in a 250 ml Parr Shaker using 0.17 g of 5% palladium on carbon (water wet) per 0.1 mole of acetamide **9** slurried in 212 ml of methanol.

The proton nmr assignments for **10** have been previously described [10].

N-[2-Methoxy-4-[(methylsulfonyl)amino]phenyl]acetamide (**11**).

The dichloromethane solution of *N*-(4-amino-2-methoxyphenyl)acetamide (**10**) above was stirred under nitrogen and treated with 593 ml (7.332 moles) of pyridine. The solution was cooled to 5° then treated dropwise over 30 minutes with 567 ml (7.32 moles) of methanesulfonyl chloride keeping the temperature below 15°. The dark red mixture was stirred in the cold then slowly warmed to 25° overnight. The pink solution was concentrated and evacuated at 80° to give a thick residue which was slurried in 4 liters of water for 30 minutes. The solids were filtered, washed with 4 liters of water, then dried under vacuum at 45° to leave 1.315 kg (90% from intermediate **9**) of crude **11** as a pink-red powder. This material was used directly in the next step.

The analytical and proton nmr data for **11** have been previously described [10].

N-(4-Amino-3-methoxyphenyl)methanesulfonamide (**5**).

A 12 liter flask was charged with a suspension of 1.315 kg (5.09 moles) of the crude *N*-[2-methoxy-4-[(methylsulfonyl)amino]phenyl]acetamide (**11**) above, 4.6 liters of 95% ethanol, 1.3 liters of water, and 1.48 liters of concentrated hydrochloric acid. The stirred mixture was heated at reflux for 5 hours, then slowly cooled to 25° overnight. The resultant slurry was cooled to *ca.* 10° and maintained there for 45 minutes. The solids were collected by filtration, washed with 1.5 liters of 2-propanol, air dried, then dissolved in 10 liters of water. The warm solution was clarified with 90 g of charcoal, then adjusted to *p*H 7.8 with 500 ml of concentrated ammonium hydroxide. The slurry was treated with 10 g of sodium dithionite, stored overnight, and filtered. The solids were washed with water (3 x 500 ml), then dried at 45°/4 mm/18 hours to give 905 g (82%, 74% overall from **9**) of analytically pure sulfonamide **5** as a tan solid, mp 145-146° (lit [8] mp 144-146°); tlc (system aA), R_f = 0.67; hptlc (system c), R_f = 0.54; ir (potassium bromide): 3459, 3368, 3275, 1618, 1592, 1518, 1305, 1164 cm^{-1}; pmr (d_6-dimethyl sulfoxide): 2.84 (s, 3H), 3.73 (s, 3H), 4.66 (br s, 2H, exchanges deuterium oxide), 6.58 (s, 2H), 6.69 (s, 1H), 8.99 (s, 1H, exchanges deuterium oxide).

Anal. Calcd. for $C_8H_{12}N_2O_3S$: C, 44.43; H, 5.59; N, 12.95. Found: C, 44.35; H, 5.73; N, 12.95.

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