Anticancer Anthrapyrazoles. Improved Syntheses of Clinical Agents CI-937, CI-941, and Piroxantrone Hydrochloride

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Improved processes for the synthesis of bulk quantities of the anthrapyrazole clinical agents CI-937, CI-941, and piroxantrone hydrochloride are reported. Reported also are detailed analytical and spectroscopic data for these agents and intermediates of the synthetic sequences.

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Introduction.

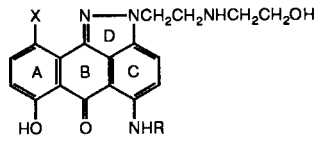
Various reports from our laboratories have detailed the design rationale, [1] synthesis, [2-4] tumor biology, [2,4,5] and biochemical pharmacology [6] of the anthrapyrazoles, a novel class of anticancer agents derived from chromophore modification of the anthracenediones related to mitoxantrone [7]. Many of these studies have been summarized in two recent reviews [8,9]. Because of their unique biochemistry and exceptional preclinical *in vivo* anticancer activity, three agents CI-937 (**1**), CI-941 (**2**), and piroxantrone hydrochloride (**3**) have been entered into human clinical trials.

The general reaction sequences to prepare the three anthrapyrazole clinical candidates have been previously described. In this paper we report improved processes that have been utilized to synthesize clinical supplies for each anthrapyrazole agent, and provide detailed analytical and spectroscopic data for all target compounds and most intermediates of each synthetic sequence.

Results and Discussion.

The N-2 upper side chain for each anthrapyrazole agent **1-3** was derived from the condensation of an appropriately substituted 1,4-dichloro-9,10-anthracenedione with 2-[(2-hydrazinoethyl)amino] ethanol (**4**), which was derived from the condensation of aqueous hydrazine with 1-aziridineethanol as earlier described [3]. We have modified slightly our original procedure such that this compound can now be obtained in 94% yield and 98% purity. Each C-5 lower side chain of CI-937, piroxantrone hydrochloride, and CI-941 is derived from condensation of a 5-chloroanthrapyrazole with diamines **5-7**, respectively. We originally synthesized protected diamine **5** by a literature procedure, [10] but found this unsuitable for scale-up operations. A much simpler method was to condense *N*-benzylmethylamine with 37% formalin and sodium cyanide under standard literature conditions [11] to give *N*-(benzyl)methylaminoacetonitrile which was reduced under high pressure over Raney cobalt [12] to provide **5** in 71% overall yield and 98% purity. The improved synthetic procedures for **4** and **5** are detailed in the Experimental. Diamines **6** and **7** were commercially available.

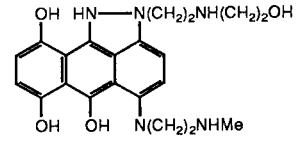
The improved synthesis of CI-937 is shown in Scheme 1. Condensation of 1,4-dichloro-5,8-bis(benzyloxy)-9,10-anthracenedione (**8**) [3] with monoalkylhydrazine **4** under modified conditions to those previously reported [3] gave the 5-chloroanthrapyrazole **9** in 53% yield. Direct condensation of **9** with neat diamine **5** at 160° gave two-armed compound **12** in 49% yield after purification by silica gel chromatography. Since chromatography was cumbersome for scale-up operations due to the marginal organic solubility of tribenzylated **12**, we opted for side chain *N*-benzylation of **9** to give 5-chloroanthrapyrazole **10** in 81% yield followed by condensation with diamine **5** to give tetrabenzylated intermediate **11** in 57% yield. Because of the enhanced organic solubility of this intermediate, we were able to purify it *via* crystallization to acceptable purity for conversion to **1**. Simultaneous hydrogenolysis of the *N*- and *O*-benzyl protecting groups in **11** or **12** was carried out over 20% palladium on carbon to provide a 94% yield of a mixture that by hplc contained 97-98% CI-937 (**1**) and 2-3% of the overreduced or "leuco" side product **13**. Hydrogenolysis of **11** under forcing conditions in an attempt to obtain complete chromophoric reduction to **13** progressed to give mixtures that contained only *ca* 20% of **13** before decomposition began to set in. Attempts to isolate a pure sample of **13** by preparative hplc chromatography were unsuccessful since **13** reoxidized to **1** under the conditions of the isolation. Hence, we assigned the structure of **13** primarily on the basis of infrared and mass spectra data. The infrared spectrum, which was derived from spectral subtraction techniques, indicated specific structural



1, X = OH; R = $CH_2CH_2NHCH_3$ (CI-937)
2, X = H; R = $CH_2CH_2NHCH_2CH_2OH$ (CI-941)
3, Y = OH; R = $CH_2CH_2CH_2NH_2$ (piroxantrone hydrochloride)

4, $NH_2NHCH_2CH_2NHCH_2CH_2OH$
5, $NH_2CH_2CH_2N(CH_3)CH_2Ph$
6, $NH_2CH_2CH_2CH_2NH_2$
7, $NH_2CH_2CH_2NHCH_2CH_2OH$

differences between **13** and CI-937 (**1**). Reduction of intensity in the 1650-1500 cm^{-1} region relative to CI-937 suggested the loss of the C=O and/or C=N functionalities of the compound. The broadened bands at 1210 cm^{-1} indicated the presence of an additional hydroxyl group and broadening of the aromatic C-H out-of-plane bending absorptions in the 800-900 cm^{-1} wavelength region suggested a loss of rigidity relative to CI-937. Mass spectral data, which were obtained from direct probe analysis of a sample enriched in **13**, gave isotope abundance ratios that were not consistent for CI-937, but indicated an excess of the M + 2 ion in addition to the molecular ion for CI-937. This distortion in the isotopic pattern was consistent with the proposed dihydro structure for **13**. In scale-up operations the presence of **13** did not cause a purification problem, but was eliminated by (a) monitoring the disappearance of **11** by hydrogen uptake and tlc, and then (b) aerating the resultant mixture over a 11-12 day period to oxidize **13** to CI-937. The purity of CI-937 following the aeration process and crystallization was 99.7% by hplc. The overall yield of CI-937 starting from commercially available 1,4-dichloro-5,8-dihydroxy-9,10-anthracenedione and proceeding *via* intermediates **8-11** was 16%.



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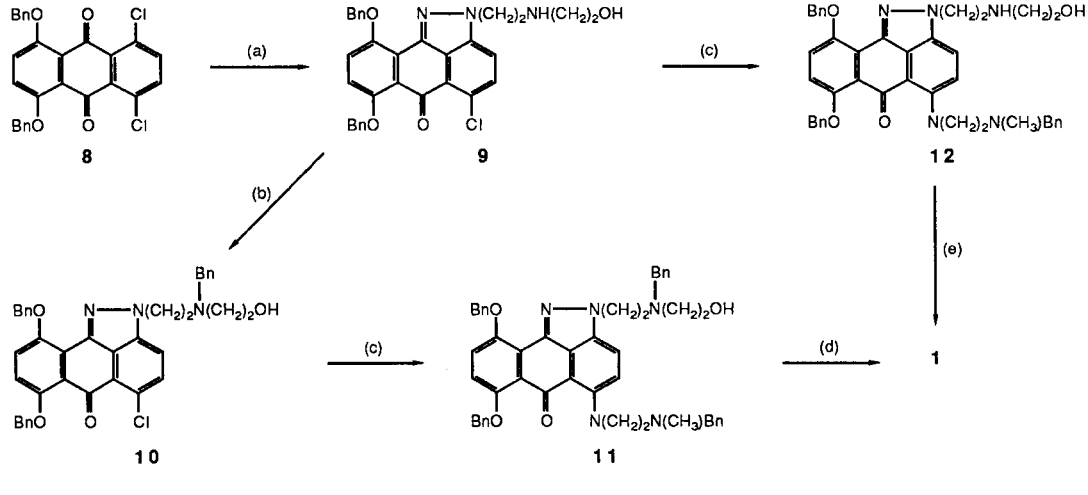
The process synthesis of piroxantrone hydrochloride (**3**) is outlined in Scheme 2 and parallels closely that described for CI-937. Condensation of either 5-chloroanthrapyrazole **9** or its side-chain *N*-benzyl analog **10** with neat 1,3-propanediamine **6** at 115-125° resulted in the two-armed penultimate intermediates **14** and **15**, respectively, in comparable yield and purity. Removal of the benzyl protecting groups of either intermediate *via* catalytic hydrogenolysis proceeded uneventfully to give **3** in good yield and purity, and without overreduction to detectable amounts of a "leuco" impurity. The overall yield of piroxantrone hydrochloride starting from 1,4-dichloro-5,8-dihydroxy-9,10-anthracenedione and proceeding *via* intermediates **8**, **9**, and **14** was 28%.

Scheme 1

Synthesis of Anthrapyrazole CI-937

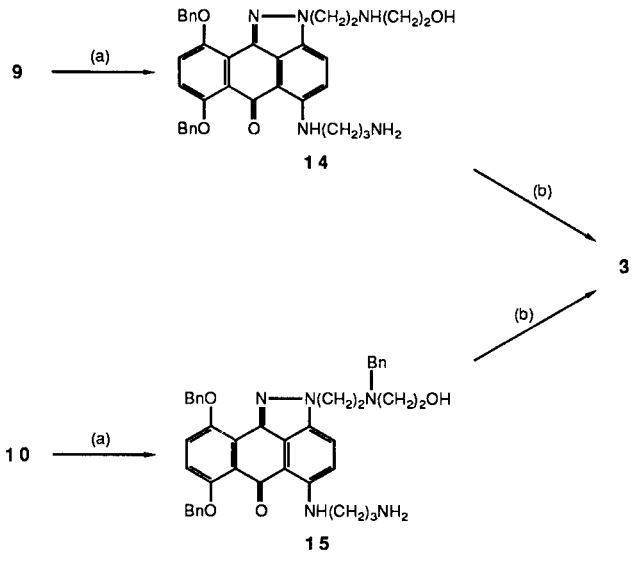


Bn = benzyl

Reagents: (a) hydrazine **4**, KF, $KHCO_3$, DMA (b) benzyl bromide, K_2CO_3, DMF (c) amine **5**, 160° (d) 20% Pd/C, H_2, CH_3OH-HOAc (3:1) (e) 20% Pd/C, H_2, HOAc.

Scheme 2

Synthesis of Piroxantrone Hydrochloride



Bn = benzyl

Reagents: (a) amine **6**, 115-125° (b) 20% Pd/C, H_2, CH_3OH-HOAc (4:1).

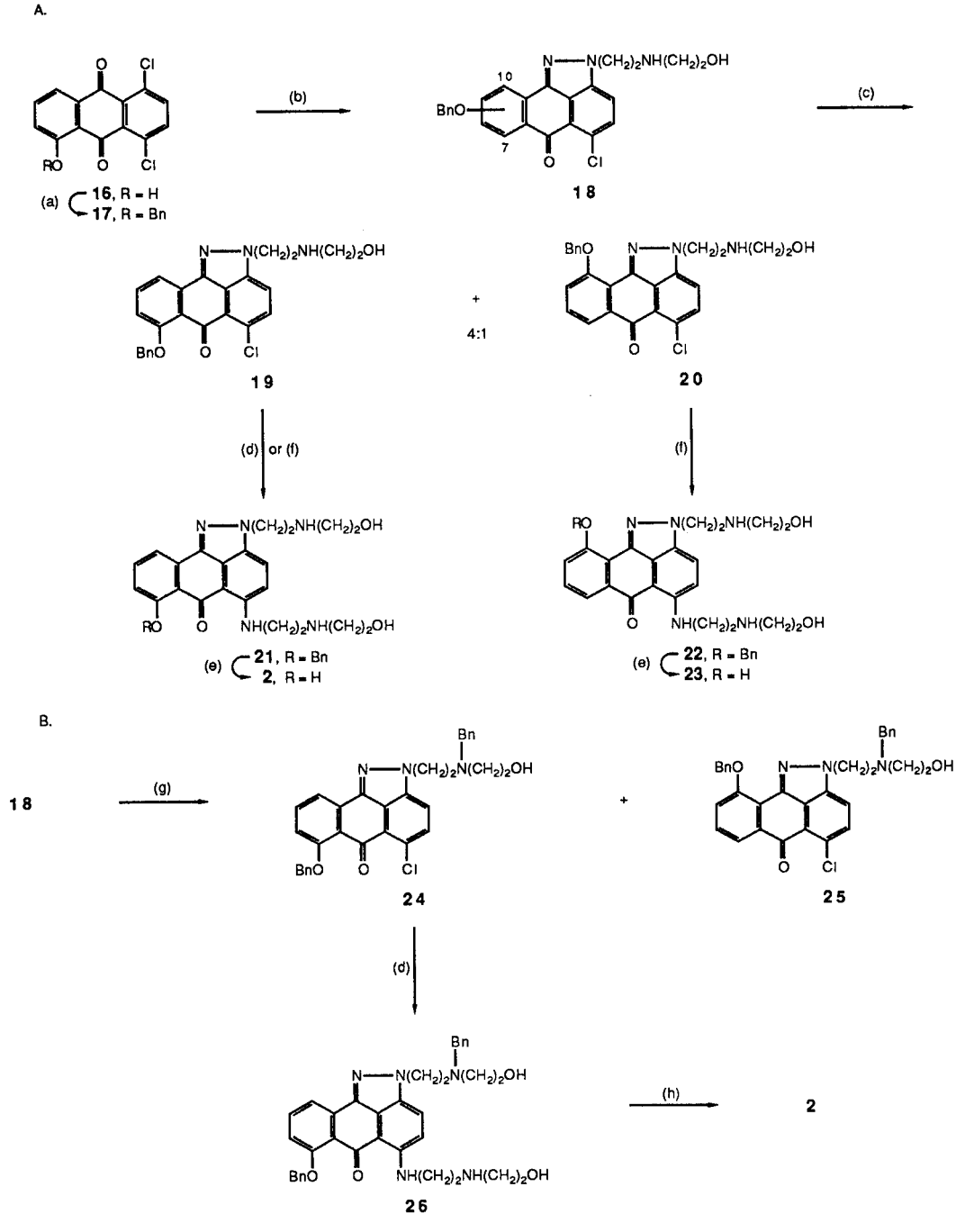
Because of the A-ring hydroxylation pattern of CI-941 (**2**), its scale-up synthesis from unsymmetrical precursor 1,4-dichloro-5-hydroxy-9,10-anthracenedione required extensive process development. The first synthetic route utilized was previously communicated [2] and is shown in Scheme 3A. Phenolic benzylation of 5-hydroxy-1,4-dichloro-9,10-anthracenedione (**16**) [13] under standard conditions gave ether **17** in 93% yield. Condensation of **17** with an excess of monoalkylhydrazine **4** was carried out either in pyridine at 80° or in dimethyl sulfoxide at 25° to give a 4:1 mixture of **19**:**20**, respectively, in variable but generally poor yield. Because of their similar mobility, only partial separation of the isomers was achieved by tedious silica gel chromatography. Subsequent condensation of each 5-chloroanthrapyrazole isomer with an excess of diamine **7** either neat at 160° or in refluxing pyridine gave the two-armed regioisomers **21** and **22** in *ca* 50% yield following purification by silica gel chromatography. Catalytic debenzylation of **21** and **22** as previously described [2] gave CI-941 (**2**) and its 10-hydroxy isomer **23**, respectively.

The first stategy to improve the CI-941 synthesis was to incorporate side chain *N*-benzylation as previously utilized for CI-937, and this is shown in Scheme 3B. Accordingly, reaction of 5-chloroanthrapyrazole mixture **18** with benzyl bromide and potassium carbonate in *N,N*-dimethylformamide gave a mixture of *N*-benzyl compounds **24** and **25** which could be more readily separated by flash silica gel chromatography than their des-*N*-benzyl congeners. Subsequent reaction of **24** with neat diamine **7** at 160° gave penultimate **26** which could be converted to CI-941 *via* catalytic debenzylation as described above. While this route led to the synthesis of a quantity of CI-941 adequate for various preclinical studies, isomer separation was still insufficient for the practical large-scale chromatography required to generate bulk drug supplies.

A second strategy, shown in Scheme 4, was evaluated to circumvent problems associated with approaches in Scheme 3. This strategy utilized a phenolic 2,4,6-trimethylbenzyl (TMB) protecting group to possibly impart greater solubility and/or more favorable differential mobility for the facile separaton of isomers **28** and **29**, either by fractional crystallization or flash silica gel chromatography. Accordingly, reaction of 2,4,6-trimethylbenzyl chloride with the cesium phenolate of 1,4-dichloro-5-hydroxy-9,10-anthracenedione (**16**) afforded a 78% yield of TMB-ether **27**. These alkylation conditions have been generalized for a series of hydroxylated 9,10-anthracenediones [14]. Subsequent reaction of **27** with hydrazine **4** in refluxing acetonitrile and catalyzed by Hunig's base gave a 4:1 mixture by hplc of regioisomers **28** and **29** in 66% yield. Use of the bulkier TMB phenolic protecting group did not enhance the regioselectivity of the hydrazine condensation. The isomers were separated cleanly by flash silica gel chromatography, but with difficulty because of their insolubility. More conveniently, a single crystallization of the mixture from *ca* 1:1 *N,N*-dimethylformamide:methanol gave a 61% recovery of **28** that was 98% pure by hplc. An additional crystallization accompanied by material losses resulted in purer **28** that still contained traces of isomer **29**. Condensation of **28** with neat amine **7** at 160° afforded two-armed compound **33** in 15% yield, the low yield attributed possibly to the thermal instability of the TMB protecting group. Because of the material losses incurred in the crystallizations described above and the poor yield of the subsequent amine condensation step, we acylated the crude mixture of regioisomers **28** and **29** with di-*t*-butyl dicarbonate to effect a clean conversion to *N*-*t*-BOC isomers **30** and **31**, respectively. These isomers possessed enhanced organic solubility and, more importantly, sufficient differential mobility that separation could easily be accomplished on a large-scale by conventional silica gel chromatography. Simultaneous cleavage of both the *N*-*t*-BOC and phenolic TMB protecting groups could be achieved by treating **30** or **31** with boron trichloride, but more conveniently for large-scale operations by gaseous hydrogen chloride in a methanol-dichloromethane mixture to afford deprotected 5-chloroanthrapyrazole isomers **32** and **34**, respectively, in excellent yield and purity. Condensation of **32** with an excess of diamine **7** in pyridine at 80° afforded CI-941 (**2**) in 73% yield and 99-100% purity by

Scheme 3

Synthesis of Anthrapyrazole CI-941 and A-Ring Isomer *Via* Benzylated Intermediates

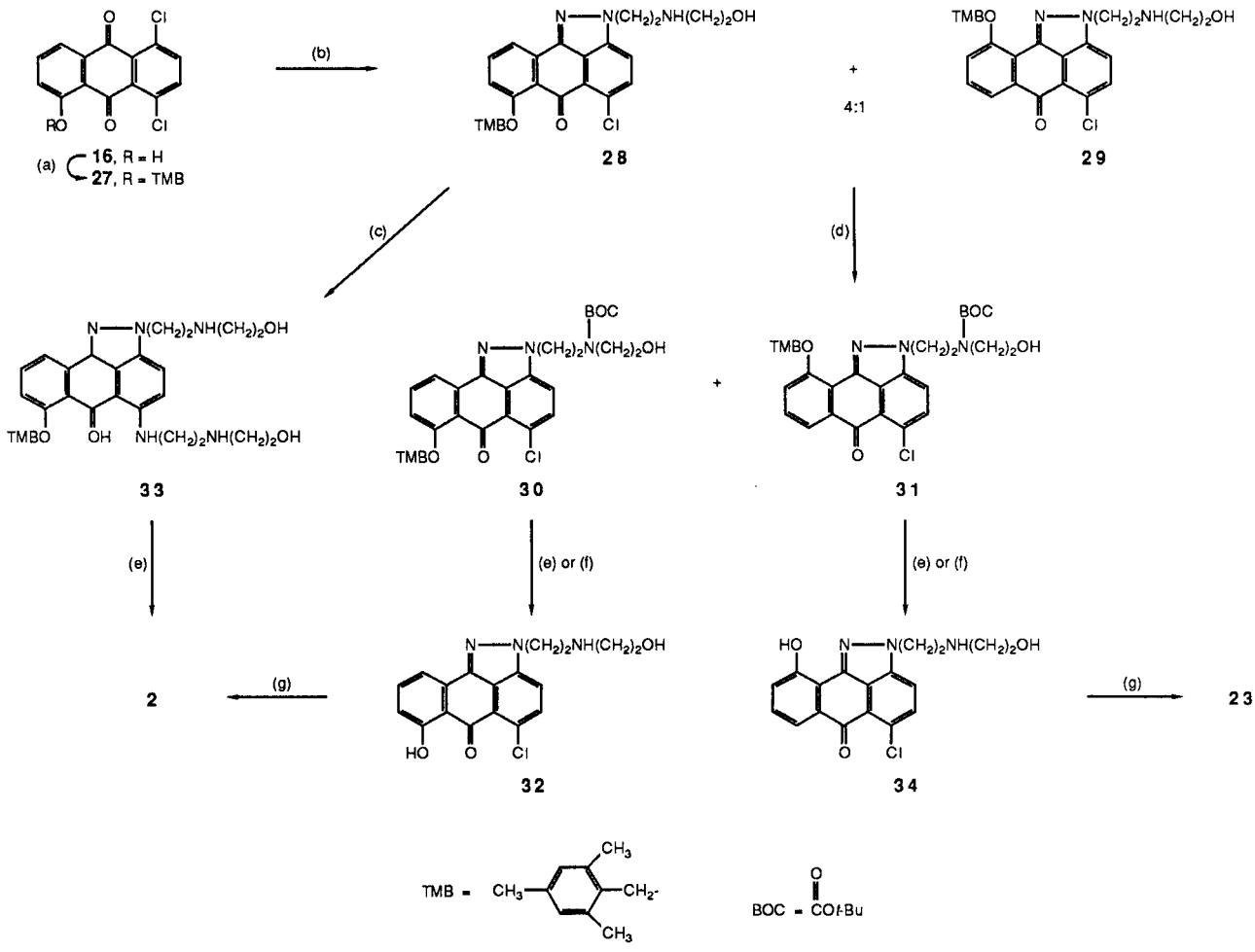


Bn = benzyl

Reagents: (a) benzyl bromide, K_2CO_3, acetone (b) hydrazine **4**, DMSO (c) SiO_2 chromatography (d) amine **7**, 160° (e) 20% $Pd(OH)_2/C$, H_2, HOAc (f) amine **7**, pyridine, reflux (g) benzyl bromide, K_2CO_3, DMF, then SiO_2 chromatography (h) 20% $Pd(OH)_2/C$, H_2, CH_3OH-HOAc (3:1).

Scheme 4

Synthesis of Anthrapyrazole CI-941 and A-Ring Isomer *Via* 2,4,6-Trimethylbenzyl Intermediates



Reagents: (a) 2,4,6-trimethylbenzyl chloride, Cs_2CO_2, acetone-DMF (3:1) (b) hydrazine **4**, $(2\text{-Pr})_2NEt$, CH_3CN (c) amine **7**, 160° (d) $(BOC)_2O$, then SiO_2 chromatography (e) HCl, CH_3OH:CH_2Cl_2 (4:1) (f) BCl_3, CH_2Cl_2 (g) amine **7**, pyridine, 80°.

hplc following hydrochloride salt formation. The overall yield of CI-941 starting from 1,4-dichloro-5-hydroxy-9,10-anthracenedione and proceeding *via* intermediates **27**, **28**, **30**, and **32** was 18%. Similar reaction of **34** provided the 10-hydroxy isomer **23** of CI-941 in comparable yield and purity.

Table I lists the ir and 200 MHz ^{1}H-nmr spectra for CI-941 (**2**), piroxantrone hydrochloride (**3**), and most of the anthrapyrazole intermediates utilized in the synthesis of the three clinical candidates. The data are in accord with the assigned structures.

Table II details the specific proton and carbon assignments for CI-937 (**1**). The proton spectra were acquired at 200 MHz. Single frequency decoupling, proton-proton two-dimensional homonuclear correlation (COSY) and single frequency NOE experiments were utilized to assign specific protons. Hence, the upper side chain OH (f) at δ 5.3 was shown to be coupled to the CH_2 (e) at δ 3.7, and the CH_2 (b') at δ 3.9 to the NH (a') at δ 8.9 and the CH_2 (c') at δ 3.2. An NOE experiment on the CH_2 (a) at δ 5.0 established the assignment of the H-3 proton at δ 8.2. The remaining side chain proton assignments were made by "walking" through the COSY spectrum.

The proton-decoupled carbon spectrum was acquired at 75 MHz. Proton-carbon heteronuclear shift correlation (HETCOR) spectra allowed assignments to be made to carbons in both side chains and to carbons 3, 4, 8, and 9 in the chromophore. The assignments made to quaternary

Table I

Spectral Properties of Anthrapyrazoles

Compound	IR (cm^{-1})	200 MHz ^{1}H-NMR (J in Hz)	^{1}H-NMR Solvent
2·2HCl	1662, 1606, 1573, 1457, 1412	3.05-3.07 (m, 14H), 4.96 (t, 2H, J = 5), 5.33 (br s, 2H, [a]), 6.85-6.94 (m, 1H), 7.42 (d, 1H, J = 6), 7.60-7.62 (m, 2H), 8.16 (d, 1H, J = 5), 8.9 (t, 1H, J = 6, [a]), 9.35-9.57 (br d, 4H [a]), 14.03 (s, 1H, [a])	DMSO-d_6 [b]
3·2HCl	1664, 1604, 1573, 1277, 1213, 1162, 825	1.96-2.06 (m, 2H), 2.94 (t, 2H, J = 7.0), 3.10 (t, 2H, J = 6.4), 3.6-3.7 (br s, 6H + HDO), 4.90 (t, 2H, J = 4.7), 6.83 (d, 1H, J = 8.9), 7.19-7.26 (m, 2H), 8.06 (d, 1H, J = 9.1)	DMSO-d_6 + D_2O
10	1655, 1451, 1273, 1211	2.80 (t, 2H, J = 5), 2.96 (t, 2H, J = 5), 3.5-3.6 (m, 4H), 4.27 (t, 1H [a]), 4.56 (t, 2H, J = 5), 5.29 (s, 2H), 5.46 (s, 2H), 6.79-6.9 (m, 6H), 6.96 (d, 1H, J = 9), 7.13 (d, 1H, J = 9), 7.2-7.4 (m, 7H), 7.5-7.62 (m, 4H)	$CDCl_3$ [c]
11	1662, 1605, 1579, 1568, 1262	2.35 (s, 3H), 2.8 (m, 4H), 3.01 (t, 3H, J = 5.5), 3.5-3.65 (m, 8H), 4.17 (br s, 1H, [a]), 4.57 (t, 2H, J = 5.5), 5.29 (s, 2H), 5.44 (s, 2H), 6.8-7.0 (m, 8H), 7.05-7.5 (m, 12H), 7.62 (t, 1H, J = 7.9), 9.62 (t, 1H, [a]), J = 5.5)	$CDCl_3$
14	1662, 1610, 1581, 1265	1.76-1.86 (m, 2H), 2.58 (t, 2H, J = 4.2), 2.72 (t, 2H, J = 6.6), 3.14 (t, 2H, J = 5), 3.37 (t, 2H, J = 5.7), 3.52 (t, 2H, J = 5.8), 4.66 (t, 2H, J = 5.6), 5.21 (s, 2H), 5.33 (s, 2H), 7.14-7.19 (m, 2H), 7.31 (d, 2H, J = 7.4), 7.37-7.43 (m, 4H), 7.60 (d, 2H, J = 7.5), 7.82-7.84 (m, 2H), 7.98 (d, 2H, J = 9.3), 9.44 (t, 1H, J = 4.6 [a])	DMSO-d_6 + D_2O
15	1662, 1605, 1567, 1266	1.72-1.85 (m, 2H), 2.59 (t, 2H, J = 6.2), 2.74 (t, 2H, J = 6.6), 3.1 (t, 2H, J = 6), 3.37 (t, 2H, J = 6.2), 3.56 (q, 2H, $J_1 = J_2 = 6.5$), 3.65 (s, 2H), 4.69 (t, 2H, J = 5), 5.24 (s, 2H), 5.31 (s, 2H), 7.06-7.96 (m, 19H), 9.46 (t, 1H, J = 5.6, [a])	DMSO-d_6
19	1659, 1592, 1562, 1286, 1211, 736	2.57 (t, 2H, J = 5.7), 3.06 (t, 2H, J = 6), 3.36 (t, 2H, J = 5.6), 4.61 (t, 2H, J = 6), 5.31 (s, 2H), 7.30-8.04 (m, 10H)	DMSO-d_6 + D_2O
20	1660, 1592, 1565, 1275, 1235, 737	2.58 (t, 2H, J = 5.8), 3.15 (t, 2H, J = 6.1), 3.36 (t, 2H, J = 5.8), 4.60 (t, 2H, J = 5.9), 5.37 (s, 2H), 7.32-8.05 (m, 10H)	DMSO-d_6 + D_2O
21	1661, 1603, 1580, 1560, 1201	1.9 (br s, 2H, [a]), 2.60 (t, 2H, J = 5.6), 2.69 (t, 2H, J = 5.8), 2.89 (t, 2H, J = 6.1), 3.07 (t, 2H, J = 6.2), 3.39 (t, 2H, J = 5.3), 3.52 (m, 4H), 4.45 (t, 1H, J = 5.1, [a]), 4.52 (t, 1H, J = 5.3, [a]), 4.60 (t, 2H, J = 5.9), 5.31 (s, 2H), 7.16-7.98 (m, 10H), 9.40 (t, 1H, J = 5.5, [a])	DMSO-d_6
22	1657, 1603, 1563, 1272	1.9 (br s, 2H, [a]), 2.60 (t, 2H, J = 5.6), 2.65 (t, 2H, J = 5.6), 2.87 (t, 2H, J = 6), 3.18 (t, 2H, J = 6.1), 3.49 (t, 2H, J = 5.6), 3.55 (m, 2H), 4.43 (br s, 1H, [a]), 4.51 (br s, 1H, [a]), 4.67 (t, 2H, J = 6.2), 5.4 (s, 2H), 7.18-8.09 (m, 10H), 9.37 (t, 1H, J = 5.6, [a])	DMSO-d_6
23·2HCl	1653, 1600, 1574, 1560, 1443, 1408	3.03-3.06 (m, 4H), 3.2 (t, 2H, J = 6), 3.5-3.7 (m, 6H), 3.9 (2H + HDO), 4.85 (br t, 2H), 7.22-7.28 (m, 2H), 7.43 (t, 1H, J = 7.9), 7.88 (d, 1H, J = 7.7), 8.01 (d, 1H, J = 9)	DMSO-d_6 + D_2O
23	1660, 1606, 1573, 1527, 1463, 1411	2.59 (t, 2H, J = 5.5), 2.67 (t, 2H, J = 5.8), 2.88 (t, 2H, J = 6.0), 3.07 (t, 2H, J = 6.1), 3.38-3.44 (m, 4H), 3.48-3.55 (m, 2H), 4.63 (t, 2H, J = 6.1), 7.19 (d, 1H, J = 9.2), 7.28 (d, 1H, J = 7.9), 7.42 (t, 1H, J = 7.9), 7.93 (d, 1H, J = 8), 8.03 (d, 1H, J = 9.1), 9.27 (t, 1H, J = 5.5, [a])	DMSO-d_6
25	1666, 1603, 1592, 1565, 1490, 1453	2.81 (t, 2H, J = 4.8), 2.97 (t, 2H, J = 5.6), 3.52 (s, 2H), 3.59 (br s, 2H), 4.1 (br s, 1H), 4.53 (t, 2H, J = 5), 5.51 (s, 2H), 6.74-6.87 (m, 5H), 7.20-7.43 (m, 7H), 7.6 (dd, 2H, J = 7.2, 1), 8.1 (dd, 1H, J = 6.9, 1)	$CDCl_3$
26	1664, 1609, 1565, 1516, 1455	2.56 (t, 2H, J = 6), 2.73 (t, 2H, J = 5.8), 2.89-2.95 (m, 2H), 3.34-3.59 (m, 12H), 4.41 (br s, 1H, [a]), 4.60 (t, 2H, J = 5.2), 5.29 (s, 2H), 6.98-7.88 (m, 15H), 9.37 (t, 1H, J = 5.7, [a])	DMSO-d_6
28	1658, 1620, 1591, 1480, 1457, 1389	2.30 (s, 3H), 2.43 (s, 6H), 2.81 (t, 2H, J = 5.1), 3.23 (t, 2H, J = 5.5), 3.61 (t, 2H, J = 4.7), 4.55 (t, 2H, J = 5.5), 5.23 (s, 2H), 6.90 (s, 2H), 7.12 (d, 1H, J = 6.6), 7.44-7.61 (m, 3H), 7.83 (d, 1H, J = 6.8)	$CDCl_3$
29	1663, 1615, 1590, 1565, 1475, 1376	2.23 (s, 3H), 2.29 (s, 6H), 2.52 (t, 2H, J = 5.8), 2.99 (t, 2H, J = 6), 3.36 (t, 2H, J = 5.6), 4.47 (t, 2H, J = 5.9), 5.27 (s, 2H), 6.88 (s, 2H), 7.52-7.68 (m, 3H), 7.92-8.06 (m, 2H)	DMSO-d_6 + D_2O

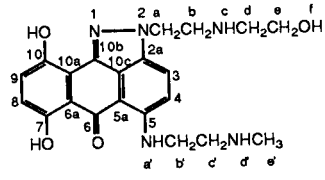
Table I (continued)

Compound	IR (cm^{-1})	200 MHz ^{1}H-NMR (J in Hz)	^{1}H-NMR Solvent
30	1673, 1590, 1564, 1457	0.94 and 1.24 (2 s, 9H), 2.30 (s, 3H), 2.43 (s, 6H), 3.1-4.69 (five br m, 8H), 5.24 (s, 2H), 6.90 (s, 2H) 7.12-7.62 (m, 4H), 7.79 (d, 1H, J = 7.1)	$CDCl_3$
31	1698, 1659, 1604, 1581, 1565, 1473, 1421, 1367	1.01 and 1.23 (2 s, 9H), 2.31 (s, 3H), 2.44 (s, 6H), 3.02-3.71 (five br m, 6H), 4.69-4.72 (br m, 2H), 5.37 (s, 2H), 6.92 (s, 2H), 7.31-7.62 (m, 4H), 8.15 (d, 1H, J = 7)	$CDCl_3$
32·HCl	1640, 1609, 1489, 1450	3.05 (t, 2H), 3.52 (t, 2H), 3.67 (t, 2H), 4.92 (t, 2H, J = 6), 5.31 (br s, 1H, [a]), 6.92 (d, 1H, J = 4), 7.43 (d, 1H, J = 3.5), 7.56-7.64 (m, 2H), 8.13 (d, 1H, J = 8.5), 9.31 (br s, 2H, [a]), 13.07 (s, 1H, [a])	DMSO-d_6
33	1664, 1609, 1566, 1516, 1549, 1398	2.28 (s, 3H), 2.39 (s, 6H), 2.71 (q, 4H, J = 5.5, 4), 2.87 (t, 2H, J = 5.5), 3.13 (t, 2H, J = 5.2), 3.40-3.48 (m, 2H), 3.62-3.71 (m, 4H), 4.45 (t, 2H, J = 5.1), 5.17 (s, 2H), 6.60 (d, 1H, J = 9.0), 6.89 (s, 2H), 7.05 (d, 1H, J = 7.5), 7.15 (d, 1H, J = 9.2), 7.52 (t, 1H, J = 8.0), 7.81 (d, 1H, J = 6.9), 9.16 (br t, 1H)	$CDCl_3$
34·HCl	1649, 1612, 1591, 1574	3.1 (t, 2H), 3.67-3.79 (m, 4H), 5.00 (t, 2H, J = 5.5), 7.36-7.49 (m, 2H), 7.72-7.82 (m, 2H), 8.19 (d, 1H, J = 8.6), 9.25 (br s, 2H, [a]), 10.18 (s, 1H, [a])	DMSO-d_6

[a] Exchanges with deuterium oxide. [b] DMSO-d_6 = dimethyl sulfoxide-d_6. [c] $CDCl_3$ = deuteriochloroform.

Table II

NMR Chemical Shift Assignments for CI-937 Hydrochloride (**1**) [a]



^{1}H Chemical Shift (δ)	^{1}H Multiplicity	^{1}H Structural Assignment	$^{13}C\{^1H\}$ Chemical Shift (ppm)	$^{13}C\{^1H\}$ Number of Attached Protons	$^{13}C\{^1H\}$ Structural Assignment
13.6	s	10-OH [b]	186.4	0	6
9.1-9.3	s	c,d'	156.7	0	10b
9.1-9.3	s	7-OH [b],2HCl	149.1 [c]	0	10
8.9	t	a'	145.5 [c]	0	7
8.2	d	3	135.6	0	5
7.4	d	4	130.4	0	2a
7.3	d	9	122.7	1	9
6.8	d	8	121.5	0	10a
5.3	t	f	121.3	1	3
5.0	t	a	116.2 [d]	0	6a
3.9	m	b'	116.2 [d]	0	5a
3.7	t	e	116.1	1	8
3.6	t	b	114.6	1	4
3.2	m	c'	103.5	0	10c
3.1	t	d	56.4	2	e
2.6	s	e'	49.3	2	d
			47.2	2	c'
			46.5	2	b
			45.6	2	a
			39.0	2	b'
			32.7	3	e'

[a] Spectra obtained in dimethyl sulfoxide-d_6. [b],[c],[d] Assignments interchangeable.

carbons in the chromophore were based on empirical trends and are more equivocal.

In summary, we have detailed much improved processes for the synthesis of bulk quantities of the anthrapyrazole clinical candidates CI-937, CI-941, and piroxantrone hydrochloride. We also have provided detailed analytical and spectroscopic data for most compounds of the synthetic sequences.

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. Proton magnetic resonance (pmr) spectra were recorded on a Varian EM-390 or XL-200 spectrometer operating at 90 MHz or 200 MHz, respectively. Carbon-13 magnetic resonance spectra and two-dimensional spectra were recorded on a Varian XL-300 spectrometer operating at 75 MHz. 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 utilizing silica gel 60, catalog no. 5789 for normal phase tlc, catalog no. 7754-3 for open column chromatography (70-230 mesh) and catalog no. 9385 for flash chromatography (230-400 mesh); (b) Analtech C-18 silica gel, catalog no. 52031 for reverse-phase tlc. Tlc solvent systems utilized include: A, acetonitrile:0.2*N* aqueous ammonium chloride (3:1); B, dichloromethane:methanol:triethylamine in the ratios of (1) 80:20:1 (2) 60:35:5; C, dichloromethane:methanol (9:1); D, ethyl acetate; (c) E. Merck silica gel 60, catalog no. 5628 for high performance tlc. Plates were predeveloped with methanol and dried. Samples were dissolved in methanol at 0.3-1.0 mg/ml and 6 μl 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 5-6.5 cm with a mixture of chloroform:methanol:triethylamine:ammonium hydroxide:*N,N*-dimethylformamide (45:35:10:5:5). The plate was then dried and scanned with a Camag Scanner I densitometer at 254 nm with a 10 nm band width.

High pressure liquid chromatography (hplc) was carried out on the following columns: A, Alltech silica gel, 10 μm; B, Zorbax C-18, 6 μm; C, Hamilton PRP-1; D, Perkin-Elmer C-18, 5 μm; and E, Altex C-18, 5 μm. Mobile phases utilized include (1) chloroform:absolute ethanol:ammonium hydroxide in the ratios of (a) 99:1:0.25, (b) 99:1:0.1, (c) 90:10:0.25, (d) 88:11:0.5; (2) tetrahydrofuran:water, 55:45; (3) acetonitrile:water:acetic acid (30:70:1) solution, 0.005*M* in Pic B (octanesulfonic acid, sodium salt); (4) a solution containing x parts of acetonitrile and y parts of a solution made from mixing 1 liter of 0.005*M* aqueous Pic B and 10 ml of acetic acid for mobile phases (a) x:y (38:62), (b) x:y (70:30), (c) x:y (27:73), (d) a gradient system starting with x:y (25:75) adjusted over 20 minutes to x:y (75:25) and maintained here for ten minutes, (e) x:y (58:42), wherein x is methanol instead of acetonitrile; (5) A solution containing x parts of acetonitrile and y parts of a solution made from mixing 7 ml of triethylamine, 1 liter of water, and 2.8 g of potassium dihydrogen phosphate with the *p*H adjusted to 2.6 with phosphoric acid for mobile phases (a) x:y (45:55) and (b) x:y (25:75), where x is methanol:acetonitrile (1:1). Flow rates for all runs were 1.0-1.5 ml/minute.

Vapor phase chromatography (vpc) was carried out on a Hewlett-Packard 5710A instrument utilizing an OV-17 column.

All solvents and reagents utilized in reactions were "reagent grade". Solvents were predried over activated 4A molecular sieves. Potassium fluoride was dried at 170°/1 mm. Charcoal refers to activated "Darco" G-60. *In vacuo* refers to 1.0-1.5 mm. All solvents were concentrated on a rotary evaporator at 30-40° (15-20 mm) unless noted otherwise.

2-[(Hydrazinoethyl)amino]ethanol (**4**).

The following preparation is an improvement of the previously reported method [3]. To 10.25 liters (17.4 moles) of a mechanically stirred solution of 54.4% aqueous hydrazine was added slowly 2.4 kg (27.55 moles) of 1-aziridineethanol. The mixture was heated at 113° for 44 hours and then concentrated *in vacuo* first at 6 mm/90° to remove most volatiles, then at <0.5 mm/100°. The residual oil was then distilled over a period of 14 days through a Pope wiped film still with a heating jacket temperature of 145-148° and a vacuum of <0.1 mm to afford 1.95 kg (94%) of **4** as a colorless, viscous oil, 98% pure by vpc.

N-Methyl-*N*-(phenylmethyl)-1,2-diaminoethane (**5**).

The following preparation is a significant improvement of the previously reported method [10]. To a stirred solution of 2.65 kg (25.5 moles) of sodium bisulfite in 5 liters of water was added rapidly 1.555 liters (20.74 moles) of 37% formalin. The resulting solution which exothermically warmed to 56° was cooled to 30°. The mixture was treated with one portion of 2.519 kg (20.8 moles) of benzylmethylamine, stirred for 2 hours without external cooling, then treated portionwise with a solution of 1.02 kg (20.75 moles) of sodium cyanide in 4 liters of water. After stirring overnight, the mixture was extracted with ether (3 × 2.5 liters), the combined ether extracts were dried (sodium sulfate then magnesium sulfate), and concentrated to an oil. Fractional distillation at <4 mm afforded 2.87 kg (86%) of *N*-methyl-*N*-(phenylmethyl)aminoacetonitrile, bp 130-133°/4 mm, 99% pure by vpc and used directly in the next step. A solution of 1.928 kg (12 moles) of *N*-methyl-*N*-(phenylmethyl)aminoacetonitrile and 386 ml (2.78 moles) of triethylamine in 2 liters of tetrahydrofuran was hydrogenated over 390 g of Raney cobalt [12] at 1300 psi and at 80° for 5 hours. The mixture was filtered, the catalyst washed with tetrahydrofuran, and the combined filtrates concentrated to give 2.03 kg of crude **5** as an oil. Fractional distillation gave 1.615 kg (82%) of **5**, bp 124-125.7°/13 mm, 98.2% pure by vpc and suitable for further use.

5-Chloro-2-[2-[(2-hydroxyethyl)amino]ethyl]-7,10-bis(phenylmethoxy)anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**9**).

The following preparation is an improvement of the previously reported method [3]. A mixture of 1.2 kg (2.45 moles) of 1,4-dichloro-5,8-bis(phenylmethoxy)-9,10-anthracenedione (**8**), 909.2 g (7.63 moles) of 2-[(2-hydrazinoethyl)amino]ethanol (**4**), 1.996 kg (34.25 moles) of potassium fluoride and 403.3 g (3.12 moles) of *N,N*-diisopropylethylamine in 7.27 liters of *N,N*-dimethylacetamide and 6.36 liters of tetrahydrofuran was stirred under nitrogen at 70° for 20 hours, then cooled to room temperature and filtered. The filtrate was poured into 31 liters of methanol and the suspension was stirred until precipitation was complete. The precipitate was collected by filtration, washed with methanol, and dried at 50°/15 mm/22 hours to provide 782 g (54%) of **9**, mp 170-171.5°, 96.1% pure by hplc (systems Ac and B4b).

Anal. Calcd. for $C_{32}H_{28}ClN_3O_4 \cdot 0.5C_4H_9NO \cdot 0.1CH_3OH$: C, 68.17; H, 5.52; N, 8.16; Cl, 5.90. Found: C, 68.15; H, 5.16; N, 8.46; Cl, 5.81.

5-Chloro-2-[2-[(2-hydroxyethyl)(phenylmethyl)amino]ethyl-7,10-bis(phenylmethoxy)anthra[1,9-*ca*]pyrazol-6(2*H*)-one (**10**).

A mechanically stirred mixture of 782 g (1.32 moles) of 5-chloro-2-[2-[(2-hydroxyethyl)amino]ethyl]-7,10-bis(phenylmethoxy)anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**9**) and 116.5 g (0.84 mole) of anhydrous potassium carbonate in 4.08 liters of *N,N*-dimethylformamide at 0-5° was treated dropwise with 198 ml (1.66 moles) of benzyl bromide. The mixture was stirred at room temperature for a total reaction time of 96 hours. An additional 11.7 ml (0.098 mole) of benzyl bromide and 11.7 g (0.085 mole) of potassium carbonate were added after 24 hours and 48 hours, respectively. The precipitate was collected by filtration, washed successively with *N,N*-dimethylformamide, acetonitrile, water, and acetonitrile then dried at 220

mm/55°/24 hours to afford 717 g (80%) of **10**, mp 180-182°, 96.5% pure by hplc (systems Aa and B4b) and suitable for further use; tlc (solvent system C), R_f = 0.66.

Anal. Calcd. for $C_{39}H_{34}ClN_3O_4 \cdot 0.4C_3H_7NO \cdot 0.4H_2O$: C, 70.94; H, 5.57; N, 7.00; Cl, 5.21. Found: C, 71.14; H, 5.42; N, 6.88; Cl, 5.56.

2-[2-[(2-Hydroxyethyl)(phenylmethyl)amino]ethyl]-5-[[2-[methyl(phenylmethyl)amino]ethyl]amino]-7,10-bis(phenylmethoxy)anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**11**).

Under a stream of nitrogen, a mechanically stirred mixture of 362 g (0.532 mole) of 5-chloro-2-[2-[(2-hydroxyethyl)(phenylmethyl)amino]ethyl]-7,10-bis(phenylmethoxy)anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**10**) and 724 g (4.4 moles) of *N*-methyl-*N*-(phenylmethyl)-1,2-diaminoethane (**5**) was heated during a 1 hour period to an internal temperature of 150° where it was maintained for 1 hour. The mixture was cooled to 100° and slowly poured into 4 liters of mechanically stirred 2-propanol. The resulting precipitate was collected by filtration, washed with 2-propanol then petroleum ether, and dried to afford 312 g (76%) of crude product. This was combined with 296 g of material obtained similarly and dissolved in a boiling mixture of 3 liters of tetrahydrofuran and 5 liters of acetone.

The hot solution was filtered, concentrated to 5 liters, then cooled. The solids were collected by filtration, washed with acetone then petroleum ether, and dried *in vacuo* to afford 490.7 g (61%) of **11**, mp 149-151°, 92.6% pure by hplc and of sufficient purity for further use. A sample was recrystallized from hot acetone to afford an analytically pure sample, mp 150.5-151.5°, 97.5% pure by hplc (system E5a); tlc (solvent system C), R_f = 0.43.

Anal. Calcd. for $C_{49}H_{49}N_5O_4$: C, 76.24; H, 6.40; N, 9.07. Found: C, 76.15; H, 6.65; N, 9.00.

2-[2-[(2-Hydroxyethyl)amino]ethyl]-5-[[2-[methyl(phenylmethyl)amino]ethyl]amino]-7,10-bis(phenylmethoxy)anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**12**).

Reaction was carried out as previously described [4] but at 160° for 45 minutes. Workup and chromatography gave a solid residue which was crystallized from chloroform:2-propanol to give a 49% yield of pure **12**, mp 147-151°; tlc (silica gel, solvent system B1), R_f = 0.38.

7,10-Dihydroxy-2-[2-[(2-hydroxyethyl)amino]ethyl]-5-[[(2-methylamino)ethyl]amino]anthra[1,9-*cd*]pyrazol-6(2*H*)-one, Dihydrochloride (**1**).

A. From Compound **11**.

A solution of 144.3 g (0.187 mole) of 2-[2-[(2-hydroxyethyl)(phenylmethyl)]amino]ethyl]-5-[[2-[methyl(phenylmethyl)amino]ethyl]amino]-7,10-bis(phenylmethoxy)anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**11**) in 1.3 liters of methanol and 330 ml of acetic acid was hydrogenated for 124 minutes in a Parr shaker over 5 g of 20% palladium on carbon and under 5 psi hydrogen pressure. Progress of the hydrogenation was monitored by gas uptake and by C-18 silica gel tlc (solvent system A; R_f = 0.2 for **1**) or by hptlc (R_f = 0.26 for **1**, 0.88 for **11**, and 0.17 for **13**). The reaction mixture was filtered and the filtrate was concentrated to dryness. The residue was dissolved in 500 ml of methanol, the solution treated with 100 ml of a 27% solution of hydrogen chloride in methanol, and the resulting slurry was refrigerated for 64 hours. The solids were collected by filtration, washed with methanol, and air dried to give 86.5 g (92%) of **1**, 97.1% pure by hplc (system E5b) and containing 2% of the "leuco" side product **13**. The impure product **1** was combined with 183.1 g of impure **1** prepared similarly and dissolved in 3 liters of water. Air was bubbled into the solution at 25° for 278 hours. The solution was diluted with *ca.* 10 liters of 2-propanol and the resulting slurry stirred for 20 hours. The precipitate was collected by filtration and washed with 2-propanol then tetrahydrofuran to afford 161 g of **1**. The filtrate was concentrated to *ca.* 1 liter and diluted with 2-propanol as above to give a second crop of product which was recrystallized from 2-propanol:water (2:1) to leave an additional 85 g of **1**. The crops were combined and dried at 12 mm/70°/17 hours to give 219.7 g (75%) of **1**, mp 279-283° dec, 99.7% pure by hplc.

Anal. Calcd. for $C_{21}H_{25}N_5O_4 \cdot 2HCl \cdot H_2O$: C, 50.20; H, 5.83; N, 13.94; Cl^-, 14.11. Found: C, 50.10; H, 5.93; N, 13.84; Cl^-, 13.89.

B. From Compound **12**.

Hydrogenolysis of compound **12** was carried out essentially as described for compound **11** to provide **1**.

5-[(3-Aminopropyl)amino]-2-[2-[(2-hydroxyethyl)amino]ethyl]-7,10-bis(phenylmethoxy)anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**14**).

A mixture of 200 g (0.337 mole) of 5-chloro-2-[2-[(2-hydroxyethyl)amino]ethyl]-7,10-bis(phenylmethoxy)anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**9**) and 500 ml (6 moles) of 1,3-propanediamine (**6**) was stirred in a 120-125° oil bath for 80 minutes, cooled to 80°, then diluted with 300 ml of 2-propanol. The warm mixture was filtered and the filter cake was washed successively with portions of dichloromethane (4 × 300 ml), 5% aqueous sodium hydroxide (2 × 1 liter), and water (2 × 1 liter). After drying at 90°/0.2 mm there remained 144 g (72%) of **14**, mp 202-204°, 98.9% pure by hplc (systems B4b and D4a); tlc (solvent system B2), R_f = 0.25.

Anal. Calcd. for $C_{35}H_{37}N_5O_4 \cdot 0.3H_2O$: C, 70.40; H, 6.35; N, 11.73; H_2O, 0.91. Found: C, 70.37; H, 6.22; N, 11.71; H_2O, 0.86.

5-[(3-Aminopropyl)amino]-2-[2-[(2-hydroxyethyl)(phenylmethyl)amino]ethyl]-7,10-bis(phenylmethoxy)anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**15**).

A mixture of 410 g (0.602 mole) of 5-chloro-2-[2-[(2-hydroxyethyl)(phenylmethyl)amino]ethyl]-7,10-bis(phenylmethoxy)anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**10**) and 810 g (10.9 moles) of 1,3-diaminopropane (**6**) was heated in an oil bath at 115-120° for 2.5 hours. The mixture was cooled, the thick suspension diluted with dichloromethane, and the solids collected by filtration. The filter cake was washed with dichloromethane, air dried, then suspended in 6 liters of water. The suspension was diluted with 500 ml of 1*N* aqueous sodium hydroxide, stirred vigorously, and filtered. The precipitate was washed with water and dried at 5 mm/25°/overnight to give 325 g (79%) of **15**, mp 195-197°, 96% pure by hplc (system B4b).

Anal. Calcd. for $C_{42}H_{43}N_5O_4$: C, 73.99; H, 6.36; N, 10.27. Found: C, 73.64; H, 6.39; N, 10.49.

5-[(3-Aminopropyl)amino]-7,10-dihydroxy-2-[2[(2-hydroxyethyl)amino]ethyl]anthra[1,9-*cd*]pyrazol-6(2*H*)-one, Dihydrochloride (**3**).

A. From Compound **14**.

A mixture of 125 g (0.209 mole) of 5-[(3-aminopropyl)amino]-2-[2-[(2-hydroxyethyl)amino]ethyl]-7,10-bis(phenylmethoxy)anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**14**), 1 liter of methanol, and 250 ml of acetic acid was hydrogenated in a Parr shaker at 5 psi over 2 g of 20% palladium on carbon.

The reaction was monitored by hplc and judged complete after 21 hours. The mixture was filtered and the filtrate was concentrated to dryness. A solution of the residue in 320 ml of water and 1 liter of ethanol was warmed to 70°, treated with 60 ml of 6*N* hydrogen chloride in 2-propanol, diluted with 1 liter of ethanol and cooled. The red solids were collected by filtration, washed with ethanol and dried at 0.1 mm/60°/16 hours to give 94 g (90%) of **3**, 98% pure by hplc. Two recrystallizations from aqueous ethanol as above afforded **3**, mp 295-200° dec, 99.5% pure by hplc (systems C4c and D4e); tlc (C_{18} silica gel, solvent system A), R_f = 0.2; p*K*a (50% aqueous methanol) = 6.8, 8.8.

Anal. Calcd. for $C_{21}H_{25}N_5O_4 \cdot 1.9HCl \cdot 0.9H_2O$: C, 50.76; H, 5.82; N, 14.09; Cl^-, 13.56; H_2O, 3.30. Found: C, 50.99; H, 5.62; N, 14.10; Cl^-, 13.97; H_2O, 3.97.

B. From Compound **15**.

Hydrogenolysis was carried out essentially as described for compound **14**, except that the reaction was carried out at 50 psi of hydrogen for 5 hours. Workup as described above followed by two crystallizations from aqueous ethanol gave **3** in 57% yield, 99.8% pure by hplc.

1,4-Dichloro-5-(phenylmethoxy)-9,10-anthracenedione (**17**).

A m chanically stirred mixture of 177.2 g (0.605 mole) of 1,4-dichloro-5-hydroxy-9,10-anthracenedione (**16**) [13], 83.5 g (0.605 mole) of powdered anhydrous potassium carbonate, 79 ml (0.675 mole) of benzyl bromide, and 1.7 liters of dry acetone was heated at reflux for three days. The initial dark brown suspension changed to an olive green color signal-

ing the end of the reaction. The mixture was filtered hot and the salts were washed with hot acetone. The cooled filtrate was concentrated to *ca.* half of its volume. The yellow precipitate was collected by filtration, washed with acetone then methanol, and dried at 200 mm/50°/12 hours to leave 201.2 g (87%) of **17**, mp 122-126°.

The combined filtrates were evaporated to dryness. The residual solid was crystallized from hot acetone to afford 14.6 g (6%) of additional **17**, mp 122-126°; ir (potassium bromide): 1690, 1682, 1590, 1310, 1235, 1000 cm^{-1}; pmr (dimethyl sulfoxide-d_6): 5.26 (s, 2H), 7.20-7.63 (m, 8H), 7.70 (s, 2H).

Anal. Calcd. for $C_{21}H_{12}Cl_2O_3$: C, 65.81; H, 3.16; Cl, 18.50. Found: C, 65.55; H, 3.32; Cl, 18.40.

5-Chloro-2-[2-[(2-hydroxyethyl)amino]ethyl]-7-(phenylmethoxy)anthra-[1,9-*cd*]pyrazol-6(2*H*)-one (**19**) and 10-(Phenylmethoxy) Isomer **20**.

A mixture of 38.3 g (0.1 mole) of 1,4-dichloro-5-(phenylmethoxy)-9,10-anthracenedione (**17**), 33 g (0.277 mole) of 2-[(2-hydrazinoethyl)amino]-ethanol (**4**) and 200 ml of pyridine was stirred at 80° for 16 hours. The mixture was concentrated *in vacuo* to an oil that was distributed between dichloromethane and water. The organic layer was washed with water, dried, and concentrated to give 40.7 g of a residue **18**, showing a *ca.* 4:1 ratio of **19**:**20** that was purified by silica gel flash chromatography eluting with dichloromethane:methanol (9:1). Concentration of fractions containing the faster eluting component gave 6 g of a solid that was triturated in ethanol to leave 2.5 g of isomer **20**, mp 172-174°, 94% pure by hplc (system A1d) with 1% of isomer **19**.

Anal. Calcd. for $C_{25}H_{22}ClN_3O_3 \cdot 0.1H_2O$: C, 66.74; H, 4.97; N, 9.34; Cl, 7.92. Found: C, 66.76; H, 5.05; N, 9.35; Cl, 7.63.

Concentration of fractions containing the slower eluting component gave 6 g (35%) of a solid that was crystallized from ethanol to leave 4.6 g (10%) of isomer **19**, mp 142-143°, 98% pure by hplc with 2% of **20**.

Anal. Calcd. for $C_{25}H_{22}ClN_3O_3 \cdot 0.2H_2O$: C, 66.50; H, 5.00; N, 9.31; Cl, 7.85. Found: C, 66.45; H, 5.10; N, 9.31; Cl, 8.24.

Repetition of the above reaction was carried out on a mixture of 50.0 g (0.13 mole) of 1,4-dichloro-5-(phenylmethoxy)-9,10-anthracenedione, 46.5 g (0.39 mole) of 2-[(2-hydrazinoethyl)amino]ethanol and 300 ml of dimethyl sulfoxide at 25° for 66 hours. The mixture was poured into 2.5 liters of ice water. The gummy residue was collected by filtration then dissolved in dichloromethane. The solution was washed with water, dried, and concentrated to leave 50.1 g of a gummy residue. The residue was dissolved in 750 ml of dichloromethane:methanol (4:1) and filtered over 500 g of silica gel eluting with dichloromethane:methanol (4:1) until all of the isomeric mixture **18** had been collected. Concentration of the product fractions gave 35 g of a gum that was triturated in methanol to give 25 g of a yellow solid **18** containing **19** and **20** in a *ca.* 4:1 ratio by hplc (crude yield of **19** = *ca.* 34%). Partial separation of isomers by column chromatography was carried out as described above.

2-[2-[(2-Hydroxyethyl)amino]ethyl]-5-[[2-[(2-hydroxyethyl)amino]ethyl]-amino]-7-(phenylmethoxy)anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**21**).

A mixture of 2.2 g (4.9 mmoles) of 5-chloro-2-[2-[(2-hydroxyethyl)amino]ethyl]-7-(phenylmethoxy)anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**19**), 4.5 ml (44.5 mmoles) of 2-[(2-aminoethyl)amino]ethanol (**7**), 0.5 g of anhydrous potassium bicarbonate, and 15 ml of pyridine was stirred at reflux for 24 hours. The mixture was filtered and concentrated *in vacuo* to leave an oil that was layered with 2-propanol. A precipitate formed at 25° over a three day period. The solids were collected by filtration, then crystallized from 2-propanol to give, after drying, 1.0 g (40%) of **21**, mp 157-159°. Purification of filtrates was carried out by silica gel flash chromatography eluting with 5, 10, and 15% methanol in dichloromethane:triethylamine (99:1). Concentration of product fractions gave a solid that was triturated in 2-propanol to give 0.3 g (10%) of additional **21**, mp 157-159°.

Anal. Calcd. for $C_{29}H_{33}N_5O_4 \cdot 0.5H_2O$: C, 66.39; H, 6.53; N, 13.35. Found: C, 66.29; H, 6.33; N, 13.31.

Repetition of the above reaction was carried out on a mixture of 10.0 g (22.2 mmoles) of **19** and 38.6 g (370 mmoles) of 2-[(2-aminoethyl)amino]-ethanol (**7**) at 160° for 5 hours. The cooled mixture was diluted with 200 ml of 2-propanol and allowed to stand at 5° overnight. The solids were collected by filtration to give 10.3 g of crude **21** which was purified by silica gel chromatography eluting with dichloromethane:methanol:triethylamine:acetic acid (2:1:0.2:0.1). Concentration of product fractions gave a solid that was triturated in *ca.* 1:1 2-propanol:diethyl ether to give 7.5 g (48%) of pure **21** as a triacetic acid salt; mp 115-119°.

2-[2-[(2-Hydroxyethyl)amino]ethyl]-5-[[2-[(2-hydroxyethyl)amino]ethyl]amino]-10-(phenylmethoxy)anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**22**).

Reaction of a mixture of 2.35 g (5.2 mmoles) of 5-chloro-2-[2-[(2-hydroxyethyl)amino]ethyl]-10-(phenylmethoxy)anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**20**), 5 ml (49 mmoles) of 2-[(2-aminoethyl)amino]ethanol (**7**), 0.52 g of anhydrous potassium bicarbonate, and 20 ml of pyridine at reflux for 16 hours followed by workup as described for isomeric compound **21** gave 1.5 g (56%) of **22**, mp 178-180°.

Anal. Calcd. for $C_{29}H_{33}N_5O_4$: C, 67.55; H, 6.45; N, 13.58. Found: C, 67.52; H, 6.48; N, 13.65.

5-Chloro-2-[2-[(2-hydroxyethyl)(phenylmethyl)amino]ethyl)-7-(phenylmethoxy)anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**24**) and 10-(Phenylmethoxy) Isomer **25**.

A mixture of 14.5 g (32.3 mmoles) of 5-chloro-2-[2[(2-hydroxyethyl)]amino]ethyl]-7-(phenylmethoxy)anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**19**) and its 10-phenylmethoxy isomer **20**, *ca.* 4:1 respectively by hplc, 3.9 ml of benzyl bromide, 6.5 g of potassium bicarbonate, and 140 ml of *N,N*-dimethylformamide was stirred at room temperature for 18 hours. The mixture was diluted with 500 ml of water and extracted with three 200 ml portions of dichloromethane. The combined organic extracts were washed with water, dried, and concentrated to an oil that was purified by silica gel flash chromatography. Elution with ethyl acetate:hexane (3:2) followed by concentration of product fractions gave the faster eluting component as a solid. Crystallization from acetonitrile afforded 3.55 g of isomer **25**, mp 130-134°.

Anal. Calcd. for $C_{32}H_{28}ClN_3O_3$: C, 71.44; H, 5.25; N, 7.81; Cl, 6.59. Found: C, 71.35; H, 5.33; N, 7.85; Cl, 6.70.

Elution with ethyl acetate followed by concentration of product fractions afforded 9.2 g (66%) of the slower eluting isomer **24** as a syrup that could not be crystallized and thus was used directly in the next step.

5-[[2-[(2-Hydroxyethyl)amino]ethyl]amino]-2-[2-[(2-hydroxyethyl)(phenylmethyl)amino]ethyl]-7-(phenylmethoxy)anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**26**).

A mixture of 6.0 g (11.2 mmoles) of 5-chloro-2-[2-[(2-hydroxyethyl)-(phenylmethyl)amino]-7-(phenylmethoxy)anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**24**) and 12.2 ml (121 mmoles) of 2-[(2-aminoethyl)amino]ethanol (**7**) was heated at 160° for 24 hours. The cooled mixture was diluted with 60 ml of 2-propanol then maintained at 0-5° for several days. The precipitate was collected, washed with cold 2-propanol then diethyl ether, and dried at 200 mm/60°/18 hours to give 4.1 g (60%) of **26**, mp 134-137°, 97% pure by hplc (system A1d).

Anal. Calcd. for $C_{36}H_{39}N_5O_4 \cdot 0.3H_2O$: C, 70.75; H, 6.53; N, 11.46; H_2O, 0.88. Found: C, 70.61; H, 6.53; N, 11.50; H_2O, 1.17.

1,4-Dichloro-5-[(2,4,6-trimethylphenyl)methoxy]-9,10-anthracenedione (**27**).

A mechanically stirred mixture of 550.6 g (1.88 moles) of 1,4-dichloro-5-hydroxy-9,10-anthracenedione (**16**) [13], 413.4 g (2.14 moles) of anhydrous cesium carbonate, 444 g (2.4 moles) of 2,4,6-trimethylbenzyl chloride, 7.06 liters of acetone, and 2.31 liters of *N,N*-dimethylformamide was heated at reflux under nitrogen for 23 hours. During this period, additional portions of 2,4,6-trimethylbenzyl chloride (2.5 hours, 31.7 g; 6.5 hours, 63.4 g; 20 hours, 31.7 g) and one portion of cesium carbonate (20

hours, 4.8 g) were added. The mixture was cooled to 10°. The precipitate was collected by filtration, washed successively with hot water and methanol, then dried at 7-9 mm/50°/20 hours to leave 621 g (78%) of **27**, mp 216-218°, 97.9% pure by hplc (system D2); ir (potassium bromide): 1688, 1583, 1560, 1460, 1433, 772 cm^{-1}; pmr (deuteriochloroform): δ 2.3 (s, 3H), 2.4 (s, 6H), 5.2 (s, 2H), 6.91 (s, 2H), 7.39-7.79 (m, 5H).

Anal. Calcd. for $C_{24}H_{18}Cl_2O_3$: C, 67.78; H, 4.26; Cl, 16.67. Found: C, 67.76; H, 4.42; Cl, 16.44.

5-Chloro-2-[2-[(2-hydroxyethyl)amino]ethyl]-7-[(2,4,6-trimethylphenyl)methoxy]anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**28**) and 10-[(2,4,6-Trimethylphenyl)methoxy] Isomer (**29**).

A mechanically stirred mixture of 310 g (0.73 mole) of 1,4-dichloro-5-[(2,4,6-trimethylphenyl)methoxy]-9,10-anthracenedione (**27**), 260 g (2.19 moles) of 2-[(2-hydrazinoethyl)amino]ethanol (**4**), 381 ml (2.19 moles) of *N,N*-diisopropylethylamine, and 4.8 liters of acetonitrile was heated at reflux for 22 hours. The cooled mixture was concentrated *in vacuo* to a residual solid, showing a *ca.* 4:1 ratio of **28**:**29** by hplc (system D4d), that was triturated in water. The solids were collected by filtration, washed with methanol, and dried at 220 mm/50°/18 hours to leave 237 g of crude material which was used directly in the next step for the synthesis of carbamates **30** and **31**.

On a separate occasion, the crude product from above was dissolved in a mixture of 11.5 liters of *N,N*-dimethylformamide and 10.7 liters of methanol and the solution was stored at −17° overnight. The precipitated solids were collected by filtration, washed and dried as above to give 144 g (40% overall yield; 61% recrystallization yield) of **28**, mp 179.5-183.5°, 98.1% isomeric purity by hplc (system D4d). A 7.3 g portion of this material was further purified by flash silica gel chromatography utilizing gradient elution with methanol (0 to 10%) in chloroform. Fractions from the faster moving component were concentrated to a solid that was crystallized from chloroform:hexane to give 340 mg of **29**, mp 180-182°.

Anal. Calcd. for $C_{28}H_{28}ClN_3O_3$: C, 68.63; H, 5.76; N, 8.53; Cl, 7.24. Found: C, 68.58; H, 5.85; N, 8.29; Cl, 7.61.

Fractions from the slower moving component were concentrated to a solid that was crystallized from methanol to give 3.1 g of analytically pure **28**, mp 182-184°.

[5-Chloro-2,6-dihydro-6-oxo-7-[(2,4,6-trimethylphenyl)methoxy]anthra-[1,9-*cd*]pyrazol-2-yl](2-hydroxyethyl)carbamic Acid, 1,1-Dimethylethyl Ester (**30**) and 10-[(2,4,6-Trimethylphenyl)methoxy Isomer **31**.

A suspension of 411.5 g (0.84 mole) of crude 5-chloro-2-[2-[(2-hydroxyethyl)amino]ethyl]-7-[(2,4,6-trimethylphenyl)methoxy]anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**28**) and its C-10 isomer (**29**), *ca.* 4:1 respectively by hplc, 247.3 g (1.1 mole) of di-*t*-butyldicarbonate, and 3.4 liters of dichloromethane was stirred at room temperature for 2 hours. The dark solution was evaporated *in vacuo* to leave 825 g of a dark syrup which was dissolved in 1.5 liters of ethyl acetate:hexane (1:1). The solution was purified by silica gel chromatography (70-230 mesh, 10 kg) utilizing gradient elution with ethyl acetate:hexane (from 50:50 to 100:0). Concentration of fractions containing the faster eluting component gave a residual solid whose trituration in methanol left 82.3 g (11% overall from quinone **27**) of pure **31**, 185-187°, as a yellow solid after drying at 220 mm/50°/overnight; tlc (solvent system D), R_f = 0.42.

Anal. Calcd. for $C_{33}H_{36}ClN_3O_5$: C, 67.17; H, 6.15; N, 7.12; Cl, 6.01. Found: C, 67.31; H, 6.18; N, 7.31; Cl, 6.13.

Fractions containing the slower eluting isomer **30** were combined and concentrated *in vacuo* until crystallization started. The suspension was kept cold at 4°, then the solids were collected by filtration, washed successively with a small amount of cold ethyl acetate then hexane, and dried as above. Processing of the mother liquor gave a second crop of material. The total yield of product **30** was 281.3 g (37% overall from quinone **27**) with purity from 98.8% to 99.8% by hplc (system A1b), mp 143-145°; tlc (solvent system D), R_f = 0.26.

Anal. Calcd. for $C_{33}H_{36}ClN_3O_5$: C, 67.17; H, 6.15; N, 7.12; Cl, 6.01. Found: C, 67.37; H, 5.89; N, 7.08; Cl, 6.04.

5-Chloro-2-[2-[(2-hydroxyethyl)amino]ethyl]-7-hydroxyanthra[1,9-*cd*]pyrazol-6(2*H*)-one Hydrochloride (**32**).

(a) *Via* Hydrogen Chloride Deblocking of **30**.

Anhydrous hydrogen chloride was bubbled through a stirred, ice-cold solution of 103.5 g (0.175 mole) of [5-chloro-2,6-dihydro-6-oxo-7-[(2,4,6-trimethylphenyl)methoxy]anthra[1,9-*cd*]pyrazol-2-yl](2-hydroxyphenyl)-carbamic acid 1,1-dimethylethyl ester (**30**) and 1 liter of dichloromethane:methanol (1:4) until the temperature reached 20°. The bubbling was stopped and the mixture cooled to 6-8°. This process was repeated three times until a reddish precipitate began to form. The bubbling was stopped and the mixture was allowed to warm to room temperature. After overnight stirring the precipitate was collected by filtration, washed successively with dichloromethane then hexane, and dried at 220 mm/60°/overnight to leave 61.6 g (89%) of **32**, mp 264-266° dec, 98.3% pure by hplc (system D4d).

Anal. Calcd. for $C_{18}H_{16}ClN_3O_3 \cdot HCl$: C, 54.79; H, 4.31; N, 10.65; Cl, 17.99; Cl^- 8.99. Found: C, 54.81; H, 4.33; N, 10.41; Cl, 18.13; Cl^-, 8.76.

(b) *Via* Boron Trichloride Deblocking of **30**.

To a stirred ice-cold solution of 5 g (8 mmoles) of anthrapyrazole **30** in 16 ml of dichloromethane was added dropwise 24 ml of boron trichloride (1*M* in dichloromethane). The mixture was kept at 0-5° for 1.5 hours, then treated cautiously with 12 ml of methanol. The suspension was heated at reflux for 1 hour, cooled, and diluted with dichloromethane. The solids were filtered, washed with dichloromethane, and dried as above to leave 2.9 g (86%) of **32**, mp 251-256° dec, 94.3% pure by hplc (system D4d).

Anal. Calcd. for $C_{18}H_{16}ClN_3O_3 \cdot HCl \cdot 0.1H_2O$: C, 54.59; H, 4.38; N, 10.61; Cl, 17.90. Found: C, 54.60; H, 4.42; N, 10.77; Cl, 18.24.

2-[2-[(2-Hydroxyethyl)amino]ethyl]-5-[[2-[(2-hydroxyethyl)amino]ethyl]-amino]-7-[(2,4,6-trimethylphenyl)methoxy]anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**33**).

A mixture of 980 mg (2 mmoles) of 5-chloro-2-[2-[(2-hydroxyethyl)-amino]ethyl]-7-[(2,4,6-trimethylphenyl)methoxy]anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**28**) and 3 ml (30 mmoles) of 2-[(2-aminoethyl)amino]ethanol (**7**) was heated at 160° for 0.75 hour. The cooled mixture was distributed between water and dichloromethane. The organic phase was dried (magnesium sulfate) and evaporated to an oily residue that was dissolved in a minimum volume of hot 2-propanol. After standing at 0° for 20 hours, the solids were collected by filtration, washed with cold 2-propanol, and dried to leave 164 mg (15%) of **33**, mp 124-128°.

Anal. Calcd. for $C_{32}H_{39}N_5O_4 \cdot 0.7H_2O$: C, 67.39; H, 7.14; N, 12.28. Found: C, 67.32; H, 7.01; N, 12.47.

7-Hydroxy-2-[2-[(2-hydroxyethyl)amino]ethyl]-5-[[2-[(2-hydroxyethyl)-amino]ethyl]amino]anthra[1,9-*cd*]pyrazol-6(2*H*)-one Dihydrochloride (**2**).

(a) From Hydrogenolysis of Compound **21**.

A mixture of 3.1 g (6.0 mmoles) of 2-[2-[(2-hydroxyethyl)amino]ethyl]-5-[[2-[(2-hydroxyethyl)amino]ethyl]amino]-7-(phenylmethoxy)anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**21**) in 150 ml of glacial acetic acid was hydrogenated over 1.0 g of 20% palladium hydroxide on carbon at atmospheric pressure and at room temperature until 170 ml of hydrogen had been absorbed. The mixture was filtered through Celite and concentrated *in vacuo*. The residue was dissolved in boiling 2-propanol, the solution treated with an excess of hydrogen chloride in 2-propanol, and cooled. The red-orange precipitate was collected by filtration, washed with 2-propanol then diethyl ether, and dried at 200 mm/80°/7 hours to give 3.0 g (97%) of **2**, mp 257-262° dec; uv (methanol): 387 nm (log ε = 3.87), 464 (4.18), 491 (4.29); p*Ka* (50% aqueous methanol): 6.5, 7.8; log P (*p*H) [15]: −1.87 (1.0), −1.89 (4.0), −0.37 (7.4); hptlc [dichloromethane:acetonitrile:methanol:ammonium hydroxide (55:25:15:5)], R_f = 0.29.

Anal. Calcd. for $C_{32}H_{37}N_5O_4 \cdot 2HCl \cdot 0.6H_2O$: C, 51.71; H, 6.00; N, 13.70; Cl^-13.86. Found: C, 51.52; H, 5.78; N, 13.63; Cl^-, 14.03.

(b) From Hydrogenolysis of Compound **26**.

A mixture of 4.4 g (7.2 mmoles) of 5-[[2-[(2-hydroxyethyl)amino]ethyl]-amino]-2-[2-[(2-hydroxyethyl)(phenylmethyl)amino]ethyl]-7-(phenylmethoxy)anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**26**) in 60 ml of methanol and 20 ml of glacial acetic acid was hydrogenated over 250 mg of 20% palladium hydroxide on carbon at atmospheric pressure and at room temperature until 330 ml of hydrogen had been absorbed. The mixture was worked up as described above to give 3.6 g (100%) of **2**, mp 255-260° dec, 96.7% pure by hplc (system D3).

Anal. Calcd. for $C_{22}H_{27}N_5O_4 \cdot 2HCl \cdot 0.2H_2O$: C, 52.64; H, 5.90; N, 13.95; Cl^-, 14.12. Found: C, 52.41; H, 6.18; N, 13.85; Cl^-, 14.49.

(c) From Amine Condensation with **32**.

A solution of 3.94 g (10 mmoles) of 5-chloro-2-[2-[(2-hydroxyethyl)-amino]ethyl]-7-hydroxyanthra[1,9-*cd*]pyrazol-6(2*H*)-one (**32**), 10.5 ml (100 mmoles) of 2-[(2-aminoethyl)amino]ethanol (**7**), and 27 ml of pyridine was stirred under nitrogen at 82° for 21 hours. The mixture was cooled to 23°, diluted with 35 ml of 2-propanol, and the resultant suspension stirred at 5° for 2 hours. The precipitate was collected by filtration, washed successively with cold 2-propanol then hexane, and dried at 220 mm/60°/overnight to leave 3.4 g (80%) of analytically pure **2** as the free base, mp 149-150.5° dec, 98.5% pure by hplc (system D3).

A 3.2 g (7.5 mmoles) sample of the free base was suspended in methanol and treated with an excess of hydrogen chloride in 2-propanol. The mixture was heated to reflux then maintained at 0° for 2 hours. The precipitate was collected by filtration, washed with methanol, dried at 220 mm/60°/overnight, and allowed to equilibrate in air to afford 3.4 g (88%; 71% from **32**) of **2**, mp 271-273° dec, 99.5% pure by hplc.

Anal. Calcd. for $C_{22}H_{27}N_5O_4 \cdot 2HCl \cdot 0.8H_2O$: C, 51.51; H, 6.02; N, 13.65; Cl^-, 13.82. Found: C, 51.56; H, 5.85; N, 13.76; Cl^-, 13.69.

5-Chloro-2-[2-[(2-hydroxyethyl)amino]ethyl]-10-hydroxyanthra[1,9-*cd*]pyrazol-6(2*H*)-one Hydrochloride (**34**).

(a) *Via* Hydrogen Chloride Deblocking of **31**.

Reaction of 13.85 g (23.5 mmoles) of [5-chloro-2,6-dihydro-6-oxo-10-[(2,4,6-trimethylphenyl)methoxy]anthra[1,9-*cd*]pyrazol-2-yl](2-hydroxyethyl)carbamic acid, 1,1-dimethylethyl ester (**31**) with anhydrous hydrogen chloride as previously described for the synthesis of compound **32** gave 8.44 g (91%) of **34**, mp 284-287° dec.

Anal. Calcd. for $C_{18}H_{16}ClN_3O_3 \cdot HCl \cdot 0.1H_2O$: C, 54.59; H, 4.38; N, 10.61; Cl, 17.90. Found: C, 54.83; H, 4.16; N, 10.46; Cl, 17.64.

(b) *Via* Boron Trichloride Deblocking of **31**.

Reaction of 295 mg (0.5 mmole) of compound **31** with 1 ml of boron trichloride (1*M* in dichloromethane) as previously described for the synthesis of compound **32** gave 183 mg (91%) of **34**, mp 280-283° dec.

Anal. Calcd. for $C_{18}H_{16}ClN_3O_3 \cdot HCl \cdot 0.4H_2O$: C, 53.80; H, 4.48; N, 10.46; Cl, 17.65. Found: C, 53.86; H, 4.32; N, 10.55; Cl, 17.64.

10-Hydroxy-2-[2-[(2-hydroxyethyl)amino]ethyl]-5-[[2-[(2-hydroxyethyl)-amino]ethyl]amino]anthra[1,9-*cd*]pyrazol-6(2*H*)-one Dihydrochloride (**23**).

A. From Hydrogenolysis of Compound **22**.

Hydrogenolysis of 1.4 g (2.7 mmoles) of compound **22** under the conditions described for **21** followed by workup gave 800 mg (57%) of **23**, mp 260-267° dec; uv (methanol): 245 mm (log ϵ = 4.32), 284 (3.91), 370 (3.77), 455 (4.09), 476 (4.12).

Anal. Calcd. for $C_{22}H_{27}N_5O_4 \cdot 2.1HCl \cdot 0.8H_2O$: C, 51.16; H, 5.99; N, 13.56; Cl^-, 14.42; H_2O, 2.79. Found: C, 51.25; H, 5.94; N, 13.54; Cl^-, 14.66; H_2O, 2.90.

B. From Amine Condensation with **34**.

A solution of 8 g (20 mmoles) of 5-chloro-2-[2-[(2-hydroxyethyl)amino]-ethyl]-10-hydroxyanthra[1,9-*cd*]pyrazol-6(2*H*)-one (**34**), 21 ml (200 mmoles) of 2-[(2-aminoethyl)amino]ethanol (**7**), and 54 ml of pyridine was heated under argon at 80° for 27.5 hours. Tlc showed that substantial amount of starting material was present, so the mixture was heated at 100° for 28.5 hours to complete the reaction. Further workup as described for the synthesis of compound **3** gave 6.55 g (76%) of analytically pure free base of **23**, mp 150-154°. Treatment of 6 g of the base with hydrogen chloride in 2-propanol as previously described for compound **3** gave 6.5 g (92%, 70% from **34**) of **23**, mp 271-276° dec, 100% pure by hplc (system A1c).

Anal. Calcd. for $C_{22}H_{27}N_5O_4 \cdot 2.0HCl \cdot 0.3H_2O$: C, 52.45; H, 5.92; N, 13.90; Cl^-, 14.07. Found: C, 52.65; H, 5.82; N, 13.89; Cl^-, 13.74.

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