Heteroannulated-9,10-Anthracenediones. The Synthesis of Substituted 5- and 7-chloroanthra[1,9-*cd*]pyrazol-6(2*H*)-ones, Precursors to Anticancer Anthrapyrazoles.

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Synthetic methodologies to a number of 5- and 7-chloroanthra[1,9-*cd*]pyrazol-6(2*H*)-ones, **4** and **37** respectively, optionally substituted with side chains at N-2 and dioxy substituents in the A ring, are reported. Reported also are detailed uv, ir and ^{1}H-nmr spectroscopy for representative compounds.

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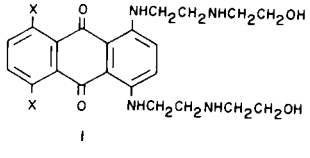
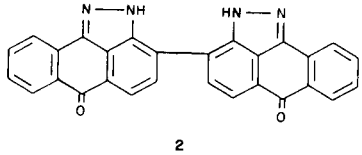
Introduction.

Recent reports from our laboratories have detailed preliminary findings for the synthesis [1], tumor biology [2], and biochemical pharmacology [3] of selected members of a novel class of anticancer agents, the 5-[(aminoalkyl)amino]substituted anthra[1,9-*cd*]pyrazol-6(2*H*)-ones (hereafter referred to as anthrapyrazoles). We designed this class of agents with the postulate that chromophore modification of the anthracenedione nucleus, such as is present in the anticancer clinical agents ametantrone (**1a**) and mitoxantrone (**1b**), might diminish cardiotoxicity by reducing the potential to from reactive oxygen species *via* semiquinone free radicals [4].



1

a, X = H, ametantrone
b, X = OH, mitoxantrone

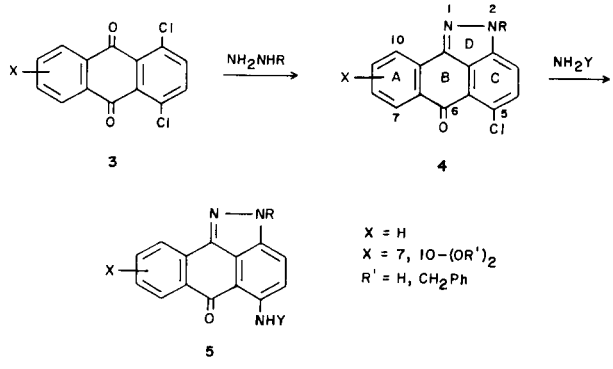


2

The anthrapyrazoles are a venerable class of compounds. The first report of their synthesis was that of Möhlau in 1912 in conjunction with the synthesis of the dyestuff pyrazoloanthrone yellow (**2**) derived from simple 9,10-anthracenedione starting materials [5]. Since then there have been numerous reports in both the patent and journal literature of the synthesis and chemistry of this commercially important class of compounds [6,7].

We detail in this paper synthetic routes to a large number of novel 5-chloroanthrapyrazoles possessing either des- or 7,10-dioxy substitution in the A-ring and the synthesis of a small number of 7-chloroanthrapyrazoles. The conversion of 5-chloro intermediates to target anthrapyrazoles is generalized in Scheme 1 and will be reported in detail elsewhere [8]. Briefly, condensation of precursor 1,4-dichloro-9,10-anthracenediones **3** with substituted monoalkyl hydrazines gives 5-chloroanthrapyrazoles **4** whose subsequent condensation with substituted primary alkylamines provides target compounds **5** with side chains extending from the N-2 and C-5 positions.

Scheme 1

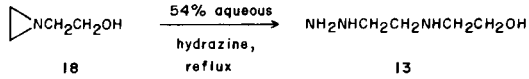


3 4 5

X = H
X = 7, 10-(OR')$_2$
R' = H, CH_2Ph

Results and Discussion.

The substituted monoalkyl hydrazines utilized in this study are listed in Table I. They were either commercially available or were synthesized by well-established literature procedures. In some cases, such as the synthesis of the hydrazines **10-12**, we made significant improvements on the reported procedures. These modifications are given in the Experimental Section. The most commonly utilized hydrazine was the novel hydrazine **13** which was easily obtained in one step from commercially available 1-aziridineethanol (**18**) in *ca.* 65% yield. Hydrazines possessing β- or γ-aminoalkyl substituents (compounds **11-17**) are especially prone to decomposition in the air at room temperature and hence must be stored under an inert gas in the cold.



18 13

Table I

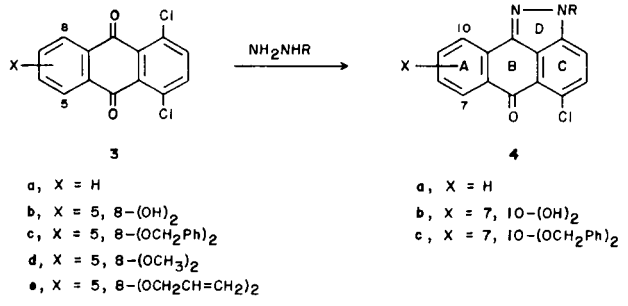
Substituted Monoalkyl Hydrazines (NH_2NHR) Utilized to Synthesize Anthrapyrazoles

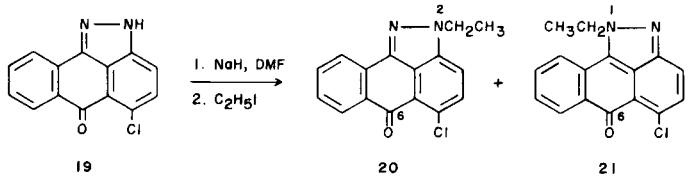
Compound	R	bp, °C	Literature Reference
6	CH_2Ph		[a]
7	$CH_2CH = CH_2$	125-127/758 mm	[9]
8	CH_2CH_2OH		[a]
9	$(CH_2)_3OH$	87-90/0.08 lit 102-104/0.6 mm	this work [10]
10	2,2-dimethyl-1,3-dioxolanyl-3-methyl-	120-124/25 mm ---	this work [11]
11	$CH_2CH_2NH_2$	81-84/15 mm lit. 87-89/16 mm	this work [12a]
12	$(CH_2)_3NH_2$	80-84/0.7 mm lit 83-84/13.5 mm	this work [13]
13	$(CH_2)_2NH(CH_2)_2OH$	110/0.05 mm	this work
14	$CH_2CH_2N(CH_3)_2$	71-72/18 mm	[14]
15	$(CH_2)_3N(CH_3)_2$	88-89/15 mm	[14]
16	$CH_2CH_2NEt_2$	76-77/7 mm	[14]
17	$CH_2CH(OH)CH_2NEt_2$	93-101/0.5-0.8 mm	[15]

[a] Commercially available

The condensation of various 1,4-dichloro-9,10-anthracenediones with the hydrazines listed in Table I is shown in Scheme 2. Compounds derived from the condensation of hydrazines with 1,4-dichloro-9,10-anthracenedione (**3a**), synthesized from leucoquinizarin by the method of Grelat [16], are listed in Table II under methods A and B. Method A generally involved the dropwise addition of the hydrazine to quinone **3a** in pyridine at the indicated temperatures. Yields of **4a** ranged from 18-86%. The condensation of **3a** with 2-[(2-hydrazineoethyl)amino]ethanol (**13**) in pyridine at 60°C however proceeded sluggishly and in poor yield. Its condensation in refluxing acetonitrile:*N,N*-dimethylformamide (method B) proceeded more cleanly giving the product in 58% yield. While these conditions have not been examined for generality, they might be preferred in cases where method A is unsatisfactory.

Scheme 2, Methods A-C





Even though each of the above reactions always gave a single chloroanthrapyrazole product, the condensation of a substituted monoalkyl hydrazine with substituted dichloro quinone **3** in principle could give one of two possible regioisomers. To address this question, we treated chloroanthrapyrazole **19** with sodium hydride in *N,N*-dimethylformamide to generate the anion delocalized on the pyrazole ring. Quenching with iodoethane gave a 3:1 mixture of regioisomers **20** and **21**, respectively.

The ir spectra of the two compounds are quite similar showing overlapping bands for the carbonyl and imine stretching frequencies of 1652 cm^{-1} and 1648 cm^{-1}, respectively, for **20**, and **21** (*vide infra*). However, the uv spectra differ dramatically. Compound **20** displays a more complex spectral pattern than **21** with a λ max of 268 nm. This is the same pattern observed for the 5-chloroanthrapyrazoles derived from the hydrazine condensations shown in Scheme 2.

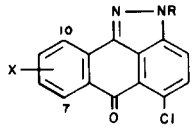
Regioisomer **21** shows a λ max of 280 nm. The ^1H-nmr of regioisomer **20** is also characteristic of anthrapyrazoles derived from the reaction of 1,4-dichloro-9,10-anthracenedione and monosubstituted hydrazines, wherein the C-7 and C-10 A-ring protons located peri to the quinone and imine moieties absorb at δ 8.12 and δ 8.39, respectively, due to the anisotropic deshielding effects of these functional groups. In contrast, regioisomer **21** shows a single downfield shift at δ 8.42 which we assign to the C-7 proton located peri to the C-6 carbonyl. The C-10 proton is located upfield relative to that of isomer **20** and is part of an aromatic five-carbon multiplet at δ 7.28-8.00. Additionally, the methylene protons α to the pyrazole nitrogen display a chemical shift value characterized of each regioisomer. Isomer **20** has a two-proton quartet at δ 4.51, a value characteristic of other members with the 6(2*H*)-one pyrazole orientation. Regioisomer **21** with the 6(1*H*)-one orientation shows a corresponding pattern at δ 4.85, a downfield shift relative to isomer **20** probably due to a deshielding effect by ring A.

Despite the strong circumstantial evidence that we had made the correct structural assignments for **20** and **21**, we obtained unequivocal evidence by X-ray analysis of a closely related derivative whose ^1H-nmr and uv spectra closely match those of structure **20** [17].

The synthesis of 5-chloroanthrapyrazoles possessing A-ring oxygenation at the 7,10-positions was investigated by several routes. The simplest and most direct procedure was to condense 5,8-dichloroquinizarin (**3b**), easily derived from the chlorination of quinizarin [18], with hydrazines in pyridine at 25-50°. (Table II, method A). This method gives good yields only for simple hydrazines. Condensa-

Table II

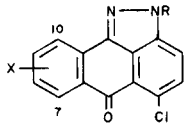
2-Substituted-5-chloroanthra[1,9-*cd*]pyrazol-6(2*H*)-ones



Compound Number	X	R	mp °C Recrystallization (trituration) solvent	Yield % [a]	Method	Reaction Conditions [b]	Molecular Formula	Analyses % Calcd./Found C	H	N	Cl	S
19	H	H	313-315 [c] ethanol	86	A	35°, 39 h, 8	$C_{14}H_7ClN_2O$	66.03 65.70	2.77 2.91	11.00 11.09	13.92 14.21	
39	H	CH_3	266-267 [d] toluene	84	A	50°, 8 h, 2	$C_{15}H_9ClN_2O$	67.05 66.72	3.38 3.67	10.43 10.54	13.19 12.96	
40	H	CH_2CH_2OH	209-211 chloroform	73	A	60°, 19 h, 3	$C_{16}H_{11}ClN_2O_2$	64.33 64.20	3.71 3.87	9.38 9.40	11.87 12.04	
41	H	$CH_2CH_2NH_2$	284-285, dec 2-propanol	35	A	25°, 4 h, 6.6	$C_{16}H_{12}ClN_3O$ [e] × HCl × 0.1 C_3H_8O × 1.2 H_2O	54.11 54.30	4.51 4.31	11.61 11.39	19.60 20.00	
42	H	$CH_2CH_2NEt_2$	263-266 [f] 2-propanol	55	A	115°, 10 h, 1.3	$C_{20}H_{20}ClN_3O$ × HCl	61.55 61.31	5.42 5.21	10.77 10.57	18.17 17.86	
43	H	$CH_2CH(OH)CH_2NEt_2$	252-254 2-propanol	18	A	40°, 6 h, 4.4	$C_{21}H_{22}N_3O_2$ × HCl × 0.3 H_2O	59.14 59.18	5.57 5.66	9.85 9.82	16.96 16.58	
44	7,10-$(OH)_2$	CH_3	298-305, dec *N,N*-dimethylformamide	72	A	35°, 14 h, 1.7	$C_{15}H_9ClN_2O_3$ × 0.1 HCl	59.20 59.08	3.01 3.13	9.20 9.05	12.81 12.73	
45	7,10-$(OH)_2$	CH_2Ph	230 *N,N*-dimethylformamide	25	A	25°, 12 da, 2.5	$C_{21}H_{13}ClN_2O_3$ [g] × 0.03 C_3H_7NO	66.83 66.44	3.52 3.81	7.51 7.50	9.35 9.74	
46	7,10-$(OH)_2$	CH_2CH_2OH	233-235 chloroform	65	A	40°, 21 h, 1.5	$C_{16}H_{11}ClN_2O_4$ × 0.25 H_2O	57.33 56.94	3.46 3.32	8.36 8.40	10.58 10.93	
47	7,10-$(OH)_2$	$CH_2CH_2NMe_2$	295-300, dec [h] (chloroform:2-propanol)	21	A	35°, 24 h, 2.1	$C_{18}H_{16}ClN_3O_3$ × 1.2 HCl × 0.8 H_2O	51.98 51.92	4.55 4.15	10.10 9.71	18.84 17.69	
48	7,10-$(OH)_2$	$(CH_2)_3NMe_2$	267-271 [i] methanol:2-propanol	22	A	37°, 10 h, 1.2	$C_{19}H_{18}ClN_3O_3$ [e] × 0.8 HCl × 0.1 C_3H_8O	56.96 56.78	4.85 4.78	10.32 10.46	15.68 15.89	
49	7,10-$(OH)_2$	$CH_2CH_2NEt_2$	280-282, dec [j] (dichloromethane: 2-propanol)	41	A [k]	50°, 4 h, 2.2	$C_{20}H_{20}ClN_3O_3$ 1.1 HCl × 0.2H_2O	55.85 55.83	5.04 4.91	9.77 9.48	17.47 17.09	
50	7,10-$(OH)_2$	$CH_2CH(OH)CH_2NEt_2$	264-267, dec [l] 2-propanol	35	A	30°, 20 h, 1.7	$C_{21}H_{22}ClN_3O_4$ × HCl × 0.7 H_2O	54.25 54.33	5.29 5.17	9.04 9.19	15.25 15.63	
51	H	$CH_2CH_2NHCH_2CH_2OH$	262-266, dec [m] methanol	58	B	82°, 4 h, 1.2	$C_{18}H_{16}ClN_3O_2$ × HCl	57.16 57.06	4.53 4.70	11.11 11.24	18.75 18.74	
52	7,10-$(OBn)_2$	$CH_2CH=CH_2$	174-177 10:1 dimethyl sulfoxide: 2-propanol	53	C	80°, 18 h, 2	$C_{31}H_{23}ClN_2O_3$	73.44 73.08	4.57 4.60	5.53 5.61	6.99 6.67	
28a	7,10-$(OBn)_2$	CH_2CH_2OH	196-198 2:1 dimethylformamide: 2-propanol	70	C	80°, 18 h, 2	$C_{30}H_{23}ClN_2O_4$ [g] × 0.2C_3H_7NO × 0.1 H_2O	69.85 69.77	4.67 4.60	5.79 6.12	6.76 6.43	
28b	7,10-$(OBn)_2$	$(CH_2)_3OH$	162-165 dimethyl sulfoxide	73	C	80°, 18 h, 2	$C_{31}H_{25}ClN_2O_4$ × 0.25 H_2O	70.32 70.20	4.85 5.09	5.29 5.67	6.70 7.06	
53	7,10-$(OBn)_2$	2,2-dimethyl-1,3-dioxolanyl-3-methyl	184-188 toluene	48	C	80°, 26 h, 3	$C_{34}H_{29}ClN_2O_5$	70.28 70.37	5.03 5.01	4.82 4.81	6.10 6.30	
54	7,10-$(OBn)_2$	$CH_2CH_2NH_2$	179-182 (2-propanol)	35	C	80°, 2 h, 3	$C_{30}H_{24}ClN_3O_3$ × 0.3 H_2O	69.91 70.04	4.81 4.81	8.15 8.14	6.88 6.86	
55	7,10-$(OBn)_2$	$(CH_2)_3NH_2$	180-184 (methanol)	17	C	80°, 6.5 h, 6	$C_{31}H_{26}ClN_3O_3$ × 0.1 HCl × 0.8H_2O	68.69 68.99	5.15 5.14	7.75 7.83	7.19 7.20	
56	7,10-$(OBn)_2$	$(CH_2)_3NH(CH_2)_2OH$	178.5-180.5 (ether)	61	C	80°, 8 h, 2	$C_{33}H_{28}ClN_3O_4$ × H_2O	67.19 67.34	5.29 5.15	7.35 7.39	6.20 6.34	
57	7,10-$(OBn)_2$	$CH_2CH_2NEt_2$	209-212 dimethyl sulfoxide	69	C	80°, 18 h, 2	$C_{34}H_{32}ClN_3O_3$ × 0.1 HCl	71.68 71.80	5.68 5.79	7.38 7.38	6.84 7.02	
58	7,10-$(OBn)_2$	$(CH_2)_3NMe_2$	196-199 (2-propanol)	35	C	70°, 6 h, 2.9	$C_{33}H_{30}ClN_3O_3$ × 0.15 H_2O	71.09 71.47	5.45 5.43	7.54 7.51	7.31 7.03	
59	7,10-$(OH)_2$	CH_2CH_2OMe	137-145, dec, (2-propanol)	78	D	4.0, 0.17	$C_{17}H_{13}ClN_2O_4$ × 0.1 HCl × 0.2 H_2O	58.01 58.39	3.87 4.03	7.96 7.89	11.08 10.81	
60	7,10-$(OH)_2$	CH_2CH_2SMe	201-203 4:1 dichloromethane: cyclohexane	31	D	2.0, 0.11	$C_{17}H_{13}ClN_2O_3S$ × 0.2 H_2O	56.00 55.99	3.71 3.52	7.68 7.57	9.72 9.95	8.79 8.82
61	7,10-$(OH)_2$	$CH_2CH_2NH_2$	265-268, dec methanol:dichloromethane	84	D	6.0, 0.09	$C_{16}H_{13}ClN_2O_3$ × HCl × 0.7 H_2O	50.78 50.95	3.83 3.95	11.10 10.87	18.64 18.54	

Table II, continued

2-Substituted-5-chloroanthra[1,9-*cd*]pyrazol-6(2*H*)-ones



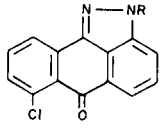
Compound Number	X	R	mp °C Recrystallization (trituration) solvent	Yield % [a]	Method	Reaction Conditions [b]	Molecular Formula	Analyses % Calcd./Found C	H	N	Cl	S
62	7,10-(OH)$_2$	$(CH_2)_2NH(CH_2)_2OH$	258-265, dec [n] methanol:dichloro-methane	75	D	4.0, 0.13	$C_{19}H_{16}ClN_3O_4$ × HCl × H_2O	50.27 49.97	4.47 4.08	9.77 9.66	16.82 16.57	
63	7,10-(OH)$_2$	$(CH_2)_3NH(CH_2)_2OH$	255-265, dec methanol:dichloro-methane	88	D	4.0, 0.17	$C_{19}H_{18}ClN_3O_4$ × 0.8 HCl × 0.75 H_2O	53.01 53.27	4.75 4.43	9.76 9.72	14.82 14.76	
64	7,10-(OH)$_2$	$(CH_2)_2N(CH_3)CH_2CH_2OH$	279-282, dec methanol:dichloro-methane	53	D	6.0, 0.1	$C_{19}H_{18}ClN_3O_4$ × 0.9 HCl × 1.9 H_2O	50.21 50.15	5.03 4.42	9.25 8.85	14.82 15.22	
65	7,10-(OH)$_2$	$(CH_2)_2NH(CH_2)_2NMe_2$	260-268, dec methanol:dichloro-methane	46	D	6.0, 0.13	$C_{20}H_{21}ClN_4O_3$ [e] × 2.0 HCl × 0.01 H_2O × 0.4 C_3H_6O	51.16 51.10	5.34 4.94	11.21 11.13	21.28 20.58	
66	7,10-(OBn)$_2$	$(CH_2)_2NHMe$	171-176 dimethyl sulfoxide	83	E	excess, 0.15	$C_{31}H_{26}ClN_3O_3$	71.06 70.74	5.00 4.99	8.02 7.73	6.77 6.71	
67	7,10-(OBn)$_2$	$(CH_2)_3NH(CH_2)_2OH$	180-184 3:1 (acetonitrile:chloroform)	87	E	10, 0.16	$C_{33}H_{30}ClN_3O_4$ × 0.5 H_2O	68.68 68.38	5.41 5.22	7.28 7.15	6.14 6.27	
68	7,10-(OBn)$_2$	$(CH_2)_2N(CH_3)CH_2CH_2OH$	191-194 (methanol)	96	E	10, 0.17	$C_{33}H_{30}ClN_3O_4$ × 0.3 H_2O	69.20 69.28	5.37 5.17	7.34 7.15	6.19 6.57	
69	7,10-(OBn)$_2$	$(CH_2)_2N(CH_2)_2NH_2$	163-166 2-propanol	66	E [o]	10, 0.17	$C_{32}H_{29}ClN_4O_3$ × 1.5 H_2O	66.24 66.10	5.56 5.66	9.66 9.26	6.11 6.63	
70	7,10-(OBn)$_2$	$(CH_2)_2NH(CH_2)_2NMe_2$	150-153 ethyl acetate	86	E	10, 0.10	$C_{34}H_{33}ClN_4O_3$ × 0.5 H_2O	69.24 68.86	5.80 5.80	9.50 9.30	6.01 6.69	

Bn = benzyl

[a] Isolated yields; generally no efforts were made to optimize these yields. [b] Methods A-C: Reaction temperature (°C); total reaction time; molar equivalents of substrate hydrazine relative to substrate 1,4-dichloro-9,10-anthracenedione. Method D: molar equivalents of boron trichloride; substrate molarity in dichloromethane after addition of boron trichloride. Method E molar equivalents of substrate amine; substrate sulfonate molarity in solvent. [c] Lit [20] mp 319°. [d] Lit [7a] mp 260°. [e] The presence of 2-propanol was demonstrated by ^{1}H-nmr. [f] free base mp = 90-92°C. [g] The presence of *N,N*-dimethylformamide was demonstrated by ^{1}H-nmr. [h] free base mp = 143-146°. [i] free base mp = 130-133°. [j] free base mp = 136-140°. [k] Prepared also in 80% yield by method D. [l] free base mp = 144-147°. [m] free base mp = 127-129°. [n] free base mp = 181-183°. [o] Prepared from mesylate **29c**.

Table III

2-Substituted-7-chloroanthra[1,9-*cd*]pyrazol-6(2*H*)-ones

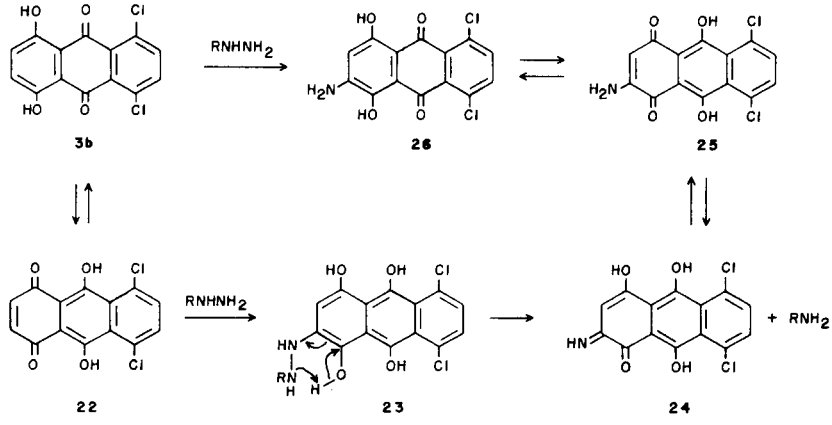


Compound Number	R	mp °C Recrystallization solvent	Yield % [a]	Method	Reaction Conditions [b]	Molecular Formula	Analyses % Calcd/Found C	H	N	Cl
71	CH_3	257-260 [c] toluene	46	A	50°, 44 h, 6.4	$C_{15}H_9ClN_2O$ × 0.1 H_2O	66.47 66.58	3.44 3.40	10.34 10.51	13.08 13.42
72	$(CH_2)_2NH(CH_2)_2OH$	272-273, dec 1:1 dichloromethane: methanol	28	B [d]	65°, 20 h, 1.7	$C_{18}H_{16}ClN_3O_2$ × HCl	57.16 56.82	4.53 4.62	11.11 11.18	18.75 19.01
73	$CH_2CH_2NEt_2$	272-275 methanol	45	A	35°, 55 h, 2.9	$C_{20}H_{20}ClN_3O$ × HCl	61.55 61.26	5.42 5.42	10.77 10.80	18.17 18.43

[a] See footnote [a], Table I. [b] See footnote [b], Table I. [c] Lit [7c] mp = 254°. [d] Acetonitrile:*N,N*-dimethylformamide volume = 2.1; [substrate quinone] = 0.13 *M*.

Scheme 3

Proposed Mechanism of Formation of 2-Amino-5,8-dichloro-1,4-dihydroxy-9,10-anthracenedione

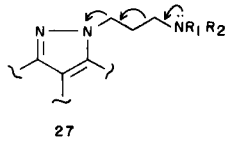


tions involving hydrazines possessing β- or γ-dialkylamino substituents gave the desired product in poor yields as well as numerous byproducts, most of which were never identified. However, in the condensation of 2-hydrazino-*N,N*-dimethylethanamine (**14**) with **3b**, we purified by silica gel chromatography a side product in 3% yield which we identified as 2-amino-5,8-dichloro-1,4-dihydroxy-9,10-anthracenedione (**26**). We propose its formation as shown in Scheme 3. Tautomerism of 5,8-dichloroquinizarin (**3b**) to its 1,4-keto isomer **22** is followed by Michael addition of the primary nitrogen of the monosubstituted hydrazine. Intramolecular proton transfer of the resultant 6-hydrazinotetrahydroxyanthracene (**23**) as shown renders the N-N bond readily cleavable with subsequent elimination of the primary alkylamine. The subsequent proton shifts lead to the observed product **26**.

We suspected that the above mentioned tautomerism of **3b** to **22** precluded the desired reaction of **3b** with the hydrazines. Indeed, we were never able to obtain but trace amounts of product in the condensation of $NH_2NH(CH_2)_2NHR$ or $NH_2NH(CH_2)_2NH_2$ with **3b**. Under a variety of reaction conditions, thin-layer chromatography showed the formation of a plethora of products. To freeze **3b** into the desired 9,10-quinone tautomer, we investigated blocking the phenolic functionality with several different groups. Accordingly, reaction of **3b** with potassium carbonate and dimethylsulfate in refluxing acetone gave the dimethoxy-9,10-anthracenedione **3d** in 92% yield. Similar reactions with allyl bromide and benzyl bromide yielded ethers **3e** and **3c** in 82% and 79% yields, respectively. We envisioned that deprotection of products derived from ethers **3d** and **3e** might be problematic, so we chose to utilize 1,4-dichloro-5,8-(dibenzyloxy)-9,10-anthracenedione (**3c**) for all subsequent condensations with hydrazines.

The use of the benzyl protecting group also vastly improved the solubility of the reaction products **4c** relative to **4b**, thus simplifying purification either by recrystallization or chromatography. The range of anthrapyrazole products synthesized from **3c** is shown in Table II under method C. We initially carried out the hydrazine condensation in refluxing pyridine, but later determined that reaction at *ca.* 80° in the dipolar aprotic solvent dimethyl sulfoxide was preferred giving the 2-substituted-5-chloro-7,10-(dibenzyloxy)anthrapyrazoles in 17-73% isolated yields. The reaction rate could generally be accelerated with the addition of anhydrous potassium fluoride.

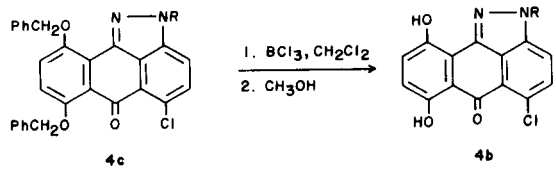
Condensations of **3c** with $NH_2NH(CH_2)_3NR_1R_2$ were not as clean or high-yielding. We ascribe this to probable degradation of the substrate hydrazine and/or derived anthrapyrazole product *via* a Grob-type fragmentation process [19] as shown in **27**.



27

Selected 5-chloro-7,10-(dibenzyloxy)anthrapyrazoles **4c** were deprotected to 7,10-dihydroxy compounds **4b** *via* reaction with boron trichloride as shown in Scheme 4. Compounds synthesized in this manner are listed in Table II under method D. Yields ranged from 31-88%. Benzyl ether cleavage *via* hydrogenolysis on 20% Pd/C in acetic acid was unsatisfactory due to concomitant cleavage of the C-5 chlorine functionality.

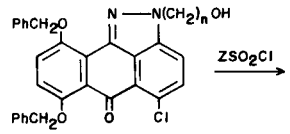
Scheme 4, Method D



4c 4b

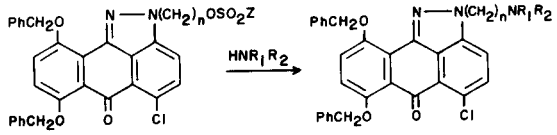
Several of our target 5-chloro-7,10-(dibenzyloxy)anthrapyrazoles could not be synthesized *via* methods B-D because the requisite hydrazines could not be made from readily available starting materials. Hence, we chose to functionalize 2- or 3-(hydroxyalkyl)-5-chloroanthrapyrazoles **28** to their sulfonate derivatives **29** which were then reacted with selected primary or secondary amines to give the elaborated products **30** in 66-96% yields as shown in Scheme 5. Compounds made by this manner are listed in Table II under method E. We found that amine condensations with tosylate **29a** were more reproducible and proceeded in higher yields than with the corresponding mesylate **29c**.

Scheme 5, Method E



28

a, n = 2
b, n = 3



29 30

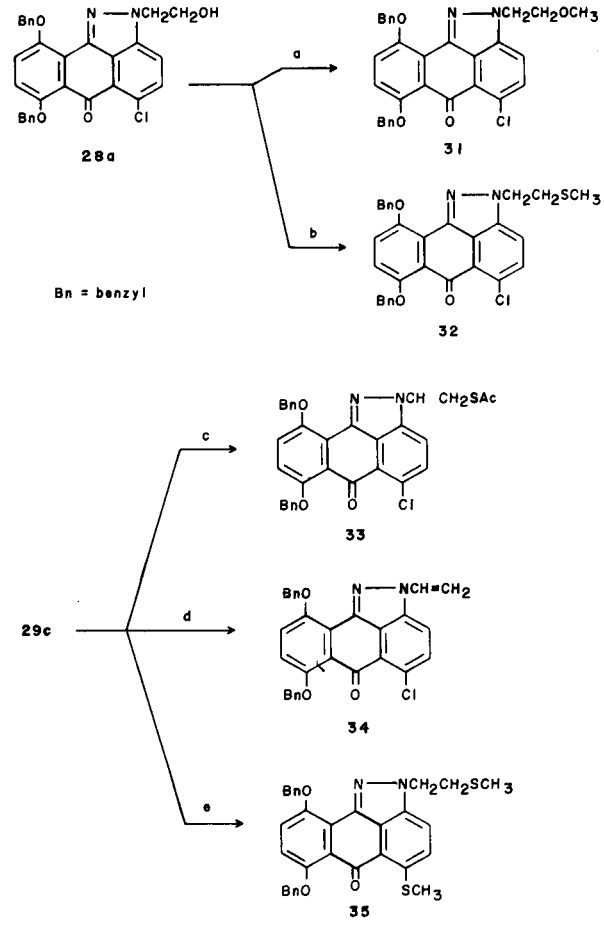
a, n = 2, Z = p-C6H4-CH3
b, n = 3, Z = p-C6H4-CH3
c, n = 2, Z = CH3

a, n = 2
b, n = 3

The synthesis of additional 2-substituted-5-chloro-7,10-(dibenzyloxy)anthrapyrazoles **31-35** from precursors **28a** and **29c** is delineated in Scheme 6. All conversions proceeded uneventfully and are detailed in the Experimental Section.

We were also interested in the synthesis of a small series of anthrapyrazoles **38** with side chains appended to the 7-position (Scheme 7). The synthesis of precursor 7-chloroanthrapyrazoles **37** from commercially available 1,5-dichloro-9,10-anthracenedione (**36**) was carried out by methods A or B. Yields were poorer than for correspoding

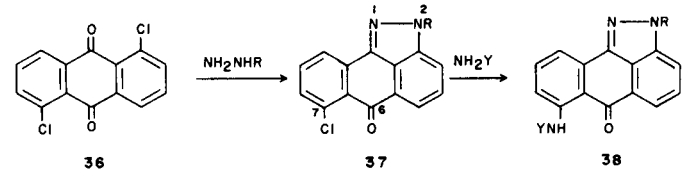
Scheme 6



(a) NaH, CH_3I, DMF. (b) CH_3SSCH_3, $n\text{-}Bu_3P$, DMF. (c) KSAc, DMF. (d) benzyltrimethylammonium methoxide, DMF. (e) CH_3SH, KF, K_2CO_3.

5-chloroanthrapyrazoles because of the apparent lower reactivity of 1,5-dichloro-9,10-anthracenedione (**36**) relative to its 1,4-isomer **3a**. The 7-chloroanthrapyrazoles synthesized are listed in Table III.

Scheme 7, Methods A and B



36 37 38

Table IV lists the spectral properties of representative A-ring nuclear variants of the 5-chloroanthrapyrazoles and a single 7-chloroanthrapyrazole. The uv spectra of the 5-and 7-chloroanthrapyrazoles unsubstituted in the A-ring each displays a unique absorption pattern with 5-6 maximum absorption bands in the 235-410 nm range (log ϵ =

Table IV

Spectral Properties of Selected 5- and 7-Chloroanthrapyrazoles

Compound Number	UV (nm) λ max (log ε)	IR (cm^{-1})	200 MHz ^{1}H-NMR (J in Hz) [a]
42·HCl	246 (4.25), 266 (4.15), 298 (4.07), 340 (3.61), 407 (3.92)	1665, 1610, 1595	1.21 (t, 6H, J = 7), 3.10-3.33 (m, 4H), 3.60-3.77 (m, 2H), 5.09 (t, 2H, J = 6.5), 7.62 (t, 1H, J = 7), 7.73-7.90 (m, 2H), 8.10 (d, 1H, J = 8), 8.26 (d, 2H, J = 8)
49·HCl	246 (4.22), 284 (3.99), 485 (4.00)	1640, 1620, 1600, 1470, 1455, 1205	1.21 (t, 6H, J = 7), 3.13-3.43 (m, 4H), 3.60-3.80 (m, 2H), 5.05 (t, 2H, J = 6.5), 6.90 (d, 1H, J = 9), 7.34 (d, 1H, J = 9), 7.71 (d, 1H, J = 9), 8.21 (d, 1H, J = 9), 9.43 (s, 1H, exchanges deuterium oxide), 10.74 (br s, 1H, exchanges deuterium oxide), 12.99 (s, 1H, exchanges deuterium oxide)
51	247 (4.23), 258 (4.12), 267 (4.15), 299 (4.04), 341 (3.57), 410 (3.91)	1649, 1610, 1586	2.62 (t, 2H, J = 6), 3.11 (t, 2H, J = 6), 3.40 (t, 2H, J = 6), 4.67 (t, 2H, J = 6), 7.63 (t, 1H, J = 9), 7.72 (d, 1H, J = 9), 7.82 (t, 1H, J = 9), 8.15-8.17 (m, 2H), 8.30 (d, 1H, J = 8)
51·HCl	—	1651, 1609, 1589	3.09 (t, 2H, J = 5), 3.58 (t, 2H, J = 6), 3.69 (q, 2H, J = 4.9, 4.8), 4.98 (t, 2H, J = 6), 5.33 (t, 1H, J = 4.8, exchanges deuterium oxide), 7.59-7.84 (m, 3H), 8.08-8.27 (m, 3H), 9.24 (broad s, 2H, exchanges deuterium oxide)
56	242 (4.41), 273 (4.05), 329 (3.76), 442 (3.98)	1660, 1575, 1450, 1270	2.62 (t, 2H, J = 6), 3.19 (t, 2H, J = 6), 3.37 (t, 2H, J = 6), 4.48 (t, 1H, exchanges deuterium oxide), 4.67 (t, 2H, J = 6), 5.26 (s, 2H), 5.37 (s, 2H), 7.30-7.73 (m, 11H), 7.85 (d overlapping d, 2H, J = 7), 8.08 (d, 1H, J = 9)
57	241 (4.43), 275 (4.09), 330 (3.79), 445 (4.01)	1660, 1588, 1574	0.95 (t, 6H, J = 7), 2.57 (q, 4H, J = 7), 4.56 (t, 2H, J = 7), 5.29 (s, 4H), 6.95-7.83 (m, 14H)
62·HCl	210 (4.56), 244 (4.24), 283 (3.96), 490 (3.93)	1640, 1610, 1590, 1465, 1450, 1200	3.00-3.23 (m, 2H), 3.43-3.80 (m, 4H), 4.95 (t, 2H, J = 6), 5.27 (br s, 1H, exchanges deuterium oxide), 6.94 (d, 1H, J = 9), 7.37 (d, 1H, J = 9), 7.76 (d, 1H, J = 9), 8.17 (d, 1H, J = 9), 9.06 (br s, 1H, exchanges deuterium oxide), 9.46 (s, 1H, exchanges deuterium oxide), 13.04 (s, 1H, exchanges deuterium oxide)
70	243 (4.33), 278 (3.91), 330 (3.77), 443 (4.05)	1660, 1570, 1450, 1270	2.03 (s, 6H), 2.22 (t, 2H, J = 6), 2.57 (t, 2H, J = 6), 3.15 (t, 2H, J = 6), 4.64 (t, 2H, J = 6), 5.21 (s, 2H), 5.31 (s, 2H), 7.23-7.70 (m, 11 H), 7.81 (d overlapping d, 2H, J = 7.5), 8.04 (d, 1H, J = 9)
72·HCl	235 (4.16), 277 (4.03), 307 (3.80), 408 (4.04)	1660, 1650, 1610, 1590, 1450	3.07 (t, 2H, J = 5), 3.50-3.77 (m, 4H), 4.97 (t, 2H, J = 6), 5.30 (t, 1H, J = 5, exchanges deuterium oxide), 7.60-7.97 (m, 4H), 8.17 (d, overlapping d, 2H, J = 8), 9.15 (br s, 2H, exchanges deuterium oxide)

[a] The ^{1}H-nmr solvent for all compounds except **57** was d_6-dimethyl sulfoxide. Compound **57** was run in deuteriochloroform.

3.57-4.25). Small differences exist for side chain variation at N-2 and for the position of the chloro substituent. 7,10-Dihydroxy substitution on the A-ring of 5-chloroanthrapyrazoles leads to simplification of this pattern with three maxima in the 244-490 nm range (log ε = 3.93-4.24). The 7,10-(dibenzyloxy) compounds likewise show four characteristic maxima in the 241-445 nm range (log ε = 3.76-4.43).

The ir spectra of the A-ring ubsubstituted 5-chloroanthrapyrazoles show two strong peaks in the 1665-1651 cm^{-1} region for some compounds with simple alkyl substituents at N-2. We ascribe these absorptions to carbonyl and imine stretching vibrations. Interestingly, compounds with basic side chains at N-2 show a single intense overlapping band for these functionalities. Two other weaker bands in the 1610-1590 cm^{-1} region are assigned to aromatic stretches. The infrared spectra of all the 7-chloroanthrapyrazoles synthesized show two strong bands at *ca.* 1660 cm^{-1} and *ca.* 1650 cm^{-1}. The 5-chloro-7,10-(dihydroxy)anthrapyrazoles show a weak band at *ca.* 1640 cm^{-1}, a band of moderate intensity in the 1620-1610 cm^{-1} range, and another weak band at *ca.* 1595 cm^{-1}. This shift to lower wave numbers relative to the deshydroxy compounds is indicative of strong intramolecular hydrogen bonding of the imine and carbonyl functionalities with the 7,10-phenolic substituents of the A-ring. The spectra of the corresponding 7,10-(dibenzyloxy) compounds more closely resemble those of the deshydroxy series with partially resolved intense bands for the carbonyl and imine stretches at 1665-1650 cm^{-1} for compounds containing simple alkyl side chains at N-2, and a single, more intense band at *ca.* 1660 cm^{-1} for N-2 side chains possessing heteroatom substitution. There is also a characteristic shoulder at 1635-1640 cm^{-1}.

The ^{1}H-nmr spectra of the A-ring unsubstituted 5-chloroanthrapyrazoles show well defined downfield multiplets

for the C-7 and C-10 A-ring protons located peri to the carbonyl and imine functionality, respectively (*vide supra*). For this and the 7,10-dioxo compounds, the pattern of the remaining aromatic protons is dependent on the nature of the N-2 sidechain and on the bascity of the distal nitrogen of those compounds possessing aminoalkyl side chains. This transannular effect will be discussed in greater detail at a later time. Also diagnostic for all the anthrapyrazoles with a two- or three-carbon side chain linked to N-2 is the well resolved triplet at *ca.* δ 4.6 for compounds in the free base form. This multiplet is assigned to the methylene protons on the carbon bonded to the N-2 pyrazole nitrogen. This value shifts downfield to δ 5.0-5.1 for the corresponding hydrochloride salt for compounds possessing basic side chains.

In summary, we have reported the synthesis and spectroscopic characterization of a large number of 5- and 7-chloroanthrapyrazoles with varying side chain substitution at N-2. The antitumor activity of several of these compounds against murine L1210 leukemia *in vitro* and P388 leukemia *in vivo* will be reported later as part of a larger study.

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, for ^{1}H. Chemical shifts are reported as δ units in parts per million downfield from internal tetramethylsilane. Combustion analyses were performed on a Perkin-Elmer 240 elemental analyzer. Water of crystallization was determind by Karl Fischer titration.

Chromatography was carried out with (a) E. Merck products utilizing silica gel 60 catalog No. 5760 for tlc, catalog No. 7734 for open column chromatography and catalog No. 9385 for flash chromatography.

All solvents and reagents were "reagent grade". Charcoal refers to activated "Darco" G-60. *In vacuo* refers to 1.0-1.5 torr. All solvents were concentrated on a rotary evaporator at 30-40° (15-20 torr) unless noted otherwise.

(2,2-Dimethyl-1,3-dioxolan-4-yl)methylhydrazine (**10**).

The following process is a slight adaptation of the literature procedure [11].

A mixture of 110.5 g (1.0 mole) of 3-chloro-1,2-propanediol, 197 ml (1.6 moles) of 2,2-dimethoxypropane, and 25 g (0.1 mole) of pyridinium *p*-toluenesulfonate was stirred at 25° overnight. Solid potassium carbonate was added and the mixture was fractionally distilled to give 121.1 g (80%) of the corresponding acetonide, bp 63-66°/27 mm.

A solution of 150.6 g (1.0 mole) of the acetonide and 320 ml (10.0 moles) of anhydrous hydrazine was stirred vigorously at 80° for 8 hours. The mixture settled into two layers upon cooling. The layers were separated and the aqueous layer was extracted with ether (4 × 100 ml). The combined ether and product layers were dried and concentrated to leave 156 g of a free-flowing oil which was fractionally distilled to give 105 g (72%) of product **10**, bp 120-124°/25 mm.

The following processes are significant improvements of the literature procedures [12a,13].

A. 2-Hydrazinoethanamine (**11**).

A 3 ℓ flask equipped with a mechanical stirrer, condensor, and dropping funnel was changed with a suspension of 282 g (2.0 moles) of 2-aminoethyl hydrogen sulfate in 750 ml of water. The stirred suspension was treated dropwise during 1.25 hours with 620 ml (10.6 moles) of 54% hydrazine hydrate. After stirring an additional 30 minutes, 600 ml of water was distilled off at 760 mm. The cooled solution was poured into a beaker containing 2 liters of thoroughly water washed Amberlyte IRA-400 (OH^-) resin and the mixture was stirred overnight. The resin was filtered, washed with 12 ℓ of water, and the combined filtrates were concentrated at 40-50°/25 mm to a residual oil that was fractionally distilled utilizing a short-path apparatus. The desired product was collected over a ~ 15° range with the purest material (92% by gc) distilling at bp 81-84°C/15 mm. Total yield of product ≥ 90% purity = 67.5 g (45%). The product is unstable at 25° and thus should be stored over nitrogen at ≤ −20°.

An attempt to prepare analytically pure material by repeated distillation resulted in extensive decomposition.

B. 3-Hydrazinopropanamine (**12**).

A filtered solution of 438 g (2.0 mmoles) of 3-bromopropanamine hydrobromide in 1 liter of water was added dropwise to an 80° solution of 600 ml of 54% hydrazine hydrate. The mixture was heated at 90-100° for 6 hours, then 500 ml of water was distilled off. The solution was concentrated to a viscous oil by repeated coevaporations with ethanol. The oil was diluted with 40% methanol in water. The solution was poured onto a column containing 4 kg of Amberlyte IRA-400 (OH^-) and the resin was then washed with several column volumes of water. The combined filtrates were concentrated to leave 155 g of a residual oil that was 86% pure by gc, and suitable for further use.

Fractional distillation of a 33 g portion gave desired product over a *ca.* 15° range with the purest material distilling at bp 80-84°/0.7 mm with *ca.* 70% recovery. The product is unstable at 25° and should be stored over nitrogen at ≤ −20°.

2-[(2-Hydrazinoethyl)amino]ethanol (**13**).

A solution of 86.8 g (1.0 mole) of 1-aziridineethanol and 400 ml of 54% aqueous hydrazine was heated at reflux for 2 days. Volatiles were removed at 50°/13 mm and then the concentrate was distilled at 142°/0.10 mm to give 80.9 g of product that was 88% pure by gc (yield based on purity correction = 60%). Careful redistillation of a small sample gave analytically pure **13**, bp 110°/0.05 mm; ir (liquid film): 3300, 2920, 2840, 1630, 1460, 1060 cm^{-1}; pmr (d_6-dimethyl sulfoxide): δ 2.4-2.7 (m, 6H), 3.18 (br s, 4-5H, exchanges deuterium oxide), 3.39 (t, 2H, J = 6 Hz).

Compound **13** is extremely hygroscopic and decomposes on prolonged heating and on standing in solution at room temperature. It should be stored at <5° under nitrogen at which temperature it solidifies.

Anal. Calcd. for $C_4H_{13}N_3O{\cdot}0.34\ H_2O$: C, 38.40; H, 11.01; N, 33.59. Found: C, 38.69; H, 11.00; N, 33.31.

1,4-Dichloro-5,8-bis(phenylmethoxy)-9,10-anthracenedione (**3c**).

A mixture of 593 g (1.5 moles) of 5,8-dichloroquinizarin (**3b**, 78% pure) [18], 590 g (3.45 moles) of benzyl bromide and 428 g (3.1 moles) of powdered, anhydrous potassium carbonate in 6.3 ℓ of acetone was heated at reflux for a total of 14 days. Additional portions of 160 g (1.18 mmoles) of powdered, anhydrous potassium carbonate and of 95 g (0.55 mole) of benzyl bromide were added after six and 12 days of heating, respectively. The reaction mixture was cooled and filtered. The filter cake was washed successively with acetone, water, methanol, and then ether to afford 699.4 g of crude product. This material was dissolved in 5 ℓ of *N,N*-dimethylformamide, the solution decolorized with charcoal, then allowed to crystallize. The solids were collected by filtration, washed successively with 360 ml of *N,N*-dimethylformamide then 800 ml of methanol, and dried at 200 mm/80° to afford 578 g (79%) of **3c**, mp 190-194°; ir (potassium bromide): 1682, 1592, 1573, 1210, 775 cm^{-1}; pmr (deuteriochloroform): δ 5.22 (s, 4H), 7.13 (s, 2H), 7.25-7.60 (m, 12H); uv (methanol): 410 mm (log ϵ = 3.65), 246 (4.42).

Anal. Calcd. for $C_{28}H_{18}Cl_2O_4$: C, 68.72; H, 3.71; Cl, 14.49. Found: C, 68.91; H, 3.92; 14.37.

1,4-Dichloro-5,8-dimethoxy-9,10-anthracenedione (**3d**).

A mixture of 43.3 g (140 mmoles) of 5,8-dichloroquinizarin (**3b**), 45 ml (476 mmoles) of dimethyl sulfate, 38.6 g (280 mmoles) of anhydrous, powdered potassium carbonate, 1.5 ml of methanol, and 700 ml of anhydrous acetone was stirred vigorously at reflux for 64 hours during which time the initial deep blue suspension became yellow signaling the end of the reaction. The hot mixture was diluted with 250 ml of water, then cooled to 25°. The yellow solids were filtered, washed extensively with water then acetone, and dried at 50°/200 mm to provide 43.5 g (92%) of **3d**, pure by ^{1}H-nmr and suitable for further use.

An 8.0 g sample of this material was dissolved in 50 ml of concentrated sulfuric acid, the solution filtered through a glass frit, then poured slowly into 400 ml of vigorously stirring water. The solids were collected by filtration, washed to neutrality with water, and dried to give 7.3 g (91% recovery) of analytically pure **3d**, mp 320-325°; ir (potassium bromide): 1684, 1570, 1283, 1261, 1210 cm^{-1}; pmr (trifluoroacetic acid): δ 4.00 (s, 6H), 7.40 (s, 2H), 7.58 (s, 2H); uv (methanol): 420 nm (log ϵ = 3.72), 246 (4.44), 228 (4.38).

Anal. Calcd. for $C_{16}H_{10}Cl_2O_4$: C, 56.99; H, 2.99; Cl, 21.03. Found: C, 56.63; H, 3.16; Cl, 20.75.

1,4-Dichloro-5,8-bis(2-propenyloxy)-9,10-anthracenedione (**3e**).

A mixture of 309 mg (1 mmole) of 5,8-dichloroquinizarin (**3b**), 0.35 ml (4 mmoles) of allyl bromide, 276 (2 mmoles) of powdered anhydrous potassium carbonate, and 6 ml of *N,N*-dimethylformamide was stirred at 65° for 66 hours. Solvent was evaporated *in vacuo* to leave a residual oil that was distributed between water and dichloromethane. The dried organic layer was evaporated to leave a yellow solid which was triturated in methanol and dried to give 320 mg (82%) of analytically pure **3e**, mp 152-154°; ir (potassium bromide): 1681, 1569, 1209, 987 cm^{-1}; pmr (deuteriochloroform): δ 4.65-4.70 (m, 4H), 5.29-5.37 (m, 2H), 5.46-5.58 (m, 2H), 5.99-6.18 (m, 2H), 7.19 (s, 2H), 7.54 (s, 2H); uv (methanol): 410 nm (log ϵ = 3.70), 246 (4.47), 228 (4.41).

Anal. Calcd. for $C_{20}H_{14}Cl_2O_4$: C, 61.72; H, 3.63; Cl, 18.22. Found: C, 61.47; H, 3.76; Cl, 18.49.

5-Chloro-2-ethylanthra[1,9-*cd*]pyrazol-6(2*H*)-one (**20**) and 5-chloro-1-ethylanthra[1,9-*cd*]pyrazol-6(1*H*)-one (**21**).

An ice cold solution of 510 mg (2 mmoles) of anthrapyrazole **19** in 15 ml of *N,N*-dimethylformamide was treated with 50 mg (2 mmoles) of oil-free sodium hydride. The mixture was warmed to 25° then treated with 0.16 ml (2 mmoles) of ethyl iodide. After stirring for 1 hour, the mixture was poured into water. The solids were collected by filtration, then purified by silica gel flash chromatography using dichloromethane as the eluting solvent. The first eluting compound afforded 300 mg of anthrapyrazole **20** as a bright yellow solid, mp 170°; ir (potassium bromide): 1652, 1608, 1592, 1355, 1235 cm^{-1}; pmr (deuteriochloroform): δ 1.60 (t, J = 7 Hz, 3H), 4.51 (q, J = 7 Hz, 2H), 7.38-7.80 (m, 4H), 8.12 (dd, J = 7 Hz, ~ 1.5 Hz, 1H), 8.39 (dd, J = 8 Hz, ~ 1.5 Hz, 1H); uv (methanol): 415 nm (log ϵ = 3.92), 340 (3.58), 299 (4.05), 268 (4.18), 259 (4.15), 247 (4.22).

Anal. Calcd. for $C_{16}H_{11}ClN_2O$: C, 67.97; H, 3.92; N, 9.91; Cl, 12.54. Found: C, 67.50; H, 3.94; N, 9.94; Cl, 12.86.

The second eluting component afforded 100 mg of anthrapyrazole **21** as a bright yellow solid, mp 176°; ir (potassium bromide): 1648, 1593, 1570, 1486, 1405 cm^{-1}; pmr (deuteriochloroform): δ 1.72 (t, J = 7 Hz, 3H), 4.85 (q, J = 7 Hz, 2H), 7.28-8.00 (m, 5H), 8.42 (dd, J = 8 Hz, ~ 1.5 Hz, 1H); uv (methanol): 433 nm (log ϵ 3.99), 348 (3.73), 304 (4.06), 280 (4.18).

2-Amino-5,8-dichloro-1,4-dihydroxy-9,10-anthracenedione (**26**).

Reaction of 5,8-dichloroquinizarin (**3b**) with 2-hydrazino-*N,N*-dimethylethanamine (**14**) according to method A gave a mixture that was purified by flash silica gel chromatography eluting first with dichloromethane then with 5% methanol in dichloromethane. Concentration of selected dichloromethane fractions left a solid whose trituration in ether provided pure **26** in 3% yield, mp > 200° dec; ir (potassium bromide): 3480, 3385, 1640, 1600, 1550, 1230 cm^{-1}; pmr (d$_6$-dimethyl sulfoxide): δ 6.23 (s, 1H), 6.98 (broad s, 2H, exchanges deuterium oxide), 7.70 (s, 2H), 13.32 (broad s, 1H, exchanges deuterium oxide), 13.78 (s, 1H, exchanges deuterium oxide).

Anal. Calcd. for $C_{14}H_7Cl_2NO_4 \cdot 0.1\ H_2O$: C, 51.71; H, 2.21; Cl, 21.80; N, 4.31. Found: C, 52.09; H, 2.51; Cl, 21.40; N, 4.24.

5-Chloro-2-[2-[[(4-methylphenyl)sulfonyl]oxy]ethyl]-7,10-bis(phenylmethoxy)anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**29a**).

An ice-cold mixture of 22 g (43 mmoles) of the 5-chloroanthrapyrazole **28a**, 12.3 g (65 mmoles) of *p*-toluenesulfonyl chloride and 170 ml of pyridine was stirred for 50 hours. The solid was filtered, washed with methanol and diethyl ether, and dried to give 10.5 g of analytically pure product, mp 203-206° dec. The filtrate was evaporated to dryness and the solid residue was triturated in chloroform:2-propanol (~ 1:1). The collected solids were triturated in boiling acetonitrile to give 9.3 g of additional dried product, mp 203-206° dec. total yield = 19.8 g (69%).

Anal. Calcd. for $C_{37}H_{29}ClN_2O_6S$: C, 66.81; H, 4.39; Cl, 5.33; N, 4.21; S, 4.82. Found: C, 67.08; H, 4.51; Cl, 5.60; N, 4.13; S, 4.91.

5-Chloro-2-[3-[[(4-methylphenyl)sulfonyl]oxy]propyl]-7,10-bis(phenylmethoxy)anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**29b**).

A mixture of 13.1 g (25 mmoles) of the 5-chloroanthrapyrazole **28b**, 9.5 g (50 mmoles) of *p*-toluenesulfonyl chloride, 9 ml (65 mmoles) of triethylamine, 150 mg of 4-dimethylaminopyridine, and 125 ml of dichloromethane was stirred at 5° for one day, then allowed to warm to room temperature. The yellow solids were collected by filtration, washed with water, methanol, and dried to give 8.8 g of analytically pure product, mp 143-146° dec. The filtrate was evaporated to dryness and the residue was triturated in hot methanol to give 5.5 g of a less pure second crop, mp 115-118°, total yield = 14.3 g (84%).

Anal. Calcd. for $C_{38}H_{31}ClN_2O_6S$: C, 67.20; H, 4.60; Cl, 5.22; N, 4.12; S, 4.72. Found: C, 67.05; H, 4.77; Cl, 5.44; N, 4.32; S, 4.95.

5-Chloro-2-[2-[(methylsulfonyl)oxy]ethyl]-7,10-bis(phenylmethoxy)anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**29c**).

An ice-cold mixture of 10.6 g (20.6 mmoles) of 5-chloroanthrapyrazole **28a**, 6.7 ml (82 mmoles) of dry pyridine, and 80 ml of chloroform (dried over alumina) was treated portionwise with 6.3 ml (82 mmoles) of methanesulfonyl chloride. The mixture was maintained at 0-50° for 40 hours, then the precipitated solids were collected by filtration and washed with methanol to give 9.6 g (79%) of the dried product, mp 198-201°; ir (potassium bromide): 1662, 1455, 1275, 1180 cm^{-1}; pmr (d$_6$-dimethyl sulfoxide): δ 3.00 (s, 3H), 4.65-5.05 (m, 4H), 5.19 (s, 2H), 5.30 (s, 2H), 7.17-7.85 (m, 13H), 7.98 (d, J = 8 Hz, 1H).

Anal. Calcd. for $C_{31}H_{25}ClN_2O_6S \cdot 0.5H_2O \cdot 0.1$ pyridine-HCl: C, 62.08; H, 4.40; Cl, 6.40; N, 4.83; S, 5.26. Found: C, 61.84; H, 4.42; Cl, 6.76; N, 4.75; S, 5.65.

5-Chloro-2-(2-methoxyethyl)-7,10-bis(phenylmethoxy)anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**31**).

An ice-cold mixture of 12.6 g (24.6 mmoles) of anthrapyrazole **28a**, 4.9 ml (78.7 mmoles) of iodomethane and 80 ml of dry *N,N*-dimethylformamide was treated with a single portion of 720 mg (30 mmoles) of sodium hydride. The bath was removed and the mixture was stirred for 2 hours. The thick suspension was diluted with 80 ml of ice-cold aqueous ammonium chloride. The solids were filtered and washed sequentially with water, 2-propanol, and ether to give 9.92 g (77%) of the dried product. Crystallization from ethyl acetate gave analytically pure **31**, mp 174-178°.

Anal. Calcd. for $C_{31}H_{25}ClN_2O_4 \cdot 0.1H_2O$: C, 70.68; H, 4.82; Cl, 6.73; N, 5.32. Found: C, 70.47; H, 4.82; Cl, 7.05; N, 5.56.

5-Chloro-2-[2-(methylthio)ethyl]-7,10-bis(phenylmethoxy)anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**32**).

An ice-cold stirred suspension of 500 mg (0.97 mmole) of chloroanthrapyrazole **28a** and 0.91 ml (10 mmoles) of methyl disulfide in 5 ml of *N,N*-dimethylformamide under argon was treated dropwise with 2.5 ml (10 mmoles) of tri-*n*-butylphosphine. The suspension was brought to room temperature and maintained there overnight. An additional 0.25 ml of methyl disulfide and 0.69 ml of tri-*n*-butylphosphine were added, the solution stirred for 3 hours, then poured in water. The precipitate was collected by filtration, washed with water, then dissolved in dichloromethane. The organic solution was washed with water, dried, and evaporated to a solid residue which was purified by flash silica gel chromatography eluting with dichloromethane. The combined product fractions were evaporated to a solid residue which was crystallized from acetonitrile to give 240 mg (46%) of dried **32**, mp 169-172°; ir (potassium bromide): 1659, 1632, 1573, 1450, 1269 cm^{-1}; pmr (deuteriochloroform): δ 2.07 (s, 3H), 3.15 (t, J = 6.5 Hz, 2H), 4.70 (t, 6.5 Hz, 2H), 5.30 (s, 4H), 6.97-7.83 (m, 14H).

Anal. Calcd. for $C_{31}H_{25}ClN_2O_3S$: C, 68.82; H, 4.66; Cl, 6.55; N, 5.18; S, 5.93. Found: C, 68.72; H, 4.69; Cl, 6.76; N, 5.16; S, 5.86.

Ethanethioic Acid, *S*-[2-[5-Chloro-6-oxo-7,10-bis(phenylmethoxy)anthra[1,9-*cd*]pyrazol-2(6*H*)-yl]ethyl] Ester (**33**).

A suspension of 7.06 g (12 mmoles) of mesylate **29c**, 2.06 g (18 mmoles) of freshly recrystallized potassium thioacetate, and 50 ml of *N,N*-dimethyl formamide was stirred at 25° for 18.5 hours. The mixture was diluted with water and the solids were filtered then washed successively with water, 2-propanol, and ether to give 6.4 g (83%) of the dried product, mp 136-138°.

Anal. Calcd. for $C_{32}H_{25}ClN_2O_4S \cdot 0.6\ DMF \cdot 0.5\ H_2O$: C, 65.29; H, 4.91; Cl, 5.68; N, 5.93; S, 5.14. Found: C, 64.93; H, 5.01; Cl, 5.84; N, 6.20; S, 5.73.

5-Chloro-2-ethenyl-7,10-bis(phenylmethoxy)anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**34**).

A suspension of 290 mg (0.5 mmole) of mesylate **29c**, 0.27 ml (0.6 mmole) of 40% benzyltrimethylammonium methoxide in methanol, and 2 ml of *N,N*-dimethylformamide was stirred at 25° for 1 hour. The suspension was filtered, the solids washed sequentially with water, 2-propanol, and ether to leave 200 mg (80%) of the dried product, mp 178-180°; ir (potassium bromide): 1665, 1650, 1575, 1280, 1215, 740 cm^{-1}; pmr (deuteriochloroform): δ 4.85 (d, J = 9 Hz, 1H), 5.10 (s, 2H), 5.12 (s, 2H), 5.60 (d, J = 15 Hz, 1H), 6.8-7.7 (m, 17H).

Anal. Calcd. for $C_{30}H_{21}ClN_2O_3 \cdot 0.2H_2O$: C, 72.62; H, 4.34; Cl, 7.14; N, 5.65. Found: C, 72.26; H, 4.59; Cl, 7.53; N, 5.64.

5-(Methylthio)-2-[2-(methylthio)ethyl]-7,10-bis(phenylmethoxy)anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**35**).

An ice-cold mixture of 600 mg (1 mmole) of mesylate **29c**, 20 mg of anhydrous potassium fluoride, 150 mg of anhydrous potassium carbonate, and 0.55 ml (10 mmoles) of methanethiol was heated overnight at 55° in a steel bomb. The mixture was cooled, and the solids were filtered and washed successivley with methanol and water. Crystallization from 2-methoxyethanol gave 400 mg (72%) of dried analytically pure product, mp 219-221°; ir (potasium bromide): 1650, 1630, 1270, 1210 cm^{-1}; pmr (deuteriochloroform): δ 2.00 (s, 3H), 2.56 (s, 3H), 3.08 (t, J = 7 Hz, 2H), 4.60 (t, J = 7 Hz, 2H), 5.20 (s, 4H), 6.84 (d, J = 9 Hz, 1H), 7.08 (d, J = 9 Hz, 1H), 7.10-7.70 (m, 12H).

Anal. Calcd. for $C_{32}H_{26}N_2O_3S_2 \cdot 0.3H_2O$: C, 68.95; H, 5.16; N, 5.03; S, 11.50. Found: C, 69.34; H, 5.49; N, 4.63; S, 11.18.

Method A.

(a) 5-Chloro-2-(2-hydroxyethyl)anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**40**).

A stirred mixture of 69.2 g (0.25 mole) of 1,4-dichloro-9,10-anthracenedione (**3a**) [16] and 500 ml of pyridine maintained at 60° under argon was treated dropwise over 3.5 hours with a solution of 52 ml (0.77 mole) of 2-hydrazinoethanol in 50 ml of pyridine. After stirring at 60° for a total of 19 hours, the solution was poured dropwise into 1.5 ℓ of ice water. The precipitated solids were collected by filtration, washed well with water, then dried at 100°/200 mm to afford 59.5 g (80%) of **40**, mp 200-206°. Crystallization from chloroform gave 54.5 g (73%) of analytically pure product, mp 209-211°.

(b) 5-Chloro-2-[2-(diethylamino)ethyl]-7,10-dihydroxyanthra[1,9-*cd*]pyrazole-6(2*H*)-one (**49**).

A mixture of 12.7 g (41 mmoles) of 5,8-dichloroquinizarin (**3b**) [18] and 12 g (90 mmoles) of *N,N*-diethyl-2-hydrazinoethanamine (**16**) in 65 ml of pyridine was stirred under nitrogen at 50° for 4 hours. Pyridine was evaporated *in vacuo* and the residual solid was chromatographed over 75 g of silica gel eluting with 1 ℓ of dichloromethane then 97:3 dichloromethane:methanol. Concentration of product fractions afforded 8.5 g of a solid which was crystallized from 2-propanol to give 6.5 g (41%) of pure **49** as a dark maroon solid, mp 136-140°. A solution of 1.5 g of solid in 50 ml of dichloromethane was treated with excess hydrogen chloride in 2-propanol. Crystallization provided 1.3 g of dried **49** as the hydrochloride salt mp 280-282° dec.

Method B.

5-Chloro-2-[2-[(2-hydroxyethyl)amino]ethyl]anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**51**).

A refluxing suspension of 27.7 g (100 mmoles) of 1,4-dichloro-9,10-anthracenedione (**3a**), 15 ml of triethylamine, and 500 ml of acetonitrile under argon was treated dropwise with a solution of 13.7 g (115 mmoles) of 2-[(2-hydrazinoethyl)amino]ethanol (**13**) in 30 ml of *N,N*-dimethylformamide. The mixture was maintained at reflux for 4 hours then allowed to cool to 25° overnight. The precipitate was collected by filtration, washed with 2-propanol, and dried to leave 21 g of crude product. The solids were dissolved in hot glacial acetic acid and the solution treated with excess hydrogen chloride in 2-propanol. The precipitate was filtered, washed with cold glacial acetic acid, and dried to afford 21.9 g (58%) of **51** as the hydrochloride salt, mp 262-266° dec.

Method C.

5-Chloro-2-[2-[(2-hydroxyethyl)amino]ethyl]-7,10-bis(phenylmethoxy)anthra[1,9-*cd*]pyrazol-6(2*H*)one (**56**).

A solution of 120 g (1.0 mole) of 2-[(2-hydrazinoethyl)amino]ethanol (**13**) in 200 ml of dimethyl sulfoxide (dried over 4A molecular sieves) was added dropwise to a stirred mixture of 244.7 g (0.5 mole) of 1,4-dichloro-5,8-bis(phenylmethoxy)-9,10-anthracenedione (**3c**), 50 g (0.5 mole) of powdered, anhydrous potassium bicarbonate, and 6 g (0.1 mole) of potassium fluoride (dried at 400°) at 80°. The mixture was stirred at 80° for eight hours and slowly cooled to 25° overnight. The thick, pasty precipitate was collected by filtration, washed sequentially with cold dimethyl sulfoxide, water and then ethanol, and dried at 50°/200 mm to afford 95.1 g of **56**, mp 168-170°, pure by ^1H-nmr and suitable for intermediate use.

The dimethyl sulfoxide filtrate was diluted with water and the solids collected as above to give 68.2 g of a second crop of **56**, mp 164-168°, total yield, 173.3 g (61%).

A 55 g sample of the second crop material was dissolved in a ~ 200 ml of warm *N,N*-dimethylformamide. Then silica gel 230-400 mesh was added until all of the solution had been absorbed. This mixture was chromatographed on a 1 kg column of silica gel eluting first with cyclohexane, then with dichloromethane followed by 9:1 dichloromethane:methanol. The product fractions were combined and concentrated to leave a solid residue whose trituration in ether afforded 28.2 g (51% recovery) of analytically pure **56**, mp 178.5-180.5, 99.5% pure by hplc.

Method D.

5-Chloro-7,10-dihydroxy-2-[2-[(2-hydroxyethyl)amino]ethyl]anthra[1,9-*cd*]-pyrazol-6(2*H*)-one (**62**).

To an ice-cold stirred suspension of 2.86 g (5.0 mmoles) of the 5-chloro-7,10-(dibenzyloxy)anthrapyrazole **56** in 20 ml of dry dichloromethane was added dropwise over 30 minutes 20 ml of a 1*M* solution of boron trichloride in dichloromethane. The mixture was maintained at 0-5° for 1 hour, then treated dropwise with 40 ml of methanol. The suspenson was

slowly brought to 25°, maintained there for 2 hours, then filtered. The solids were washed with methanol, then 2-propanol, and dried at 80°/200 mm overnight to give 1.6 g (75%) of **62** as a red solid, mp 258-265° dec.

A 1.02 g sample of the hydrochloride salt was suspended in 20 ml of saturated aqueous sodium bicarbonate. The mixture was heated at 60° under argon for 7 hours. The solids were collected by filtration, washed extensively with water and dried as above to leave 902 mg (90% recovery) of analytically pure **62** as the free base, mp 181-183°.

Method E.

5-Chloro-2-[2-[(2-hydroxyethyl)methylamino]ethyl]-7,10-bis(phenylmethoxy)anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**68**).

A stirred mixture of 10.0 g (15 mmoles) of tosylate **29a**, 12.1 ml (150 mmoles) of 2-(methylamino)ethanol, 4.14 g (30 mmoles) of anhydrous powdered potassium carbonate, and 90 ml of dimethyl sulfoxide was heated at 50° overnight. The mixture was maintained at 25° for 24 hours, then the solids were filtered, washed well with water, air-dried, and triturated from boiling methanol to afford 5.6 g of analytically pure **68**, mp 191-194°.

The above dimethyl sulfoxide filtrate was diluted with water and the precipitated solids processed as above to give 2.9 g of additional **68**, mp 188-192°, total yield = 8.5 g (96%).

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REFERENCES AND NOTES

[1] H. D. H. Showalter, J. L. Johnson, L. M. Werbel, W. R. Leopold, R. C. Jackson and E. F. Elslager, *J. Med. Chem.*, **7**, 253 (1984).

[2] W. R. Leopold, J. M. Nelson, J. Plowman, and R. C. Jackson, *Cancer Rec.*, **45**, 5532 (1985).

[3] D. W. Fry, T. J. Boritzki, J. A. Besserer, and R. C. Jackson, *Biochem. Pharmacol.*, **34**, 3499 (1985).

[4] H. D. H. Showalter, D. W. Fry, W. R. Leopold, J. W. Lown, J. A. Plambeck, and K. Reszka, *Anti-Cancer Drug Design*, **1**, 73 (1986).

[5] R. Möhlau, *Chem. Ber.*, **45**, 2233 (1912).

[6] O. Bayer, "Methoden der Organischen Chemie", Houben-Weyl, 4th Ed, Vol **7**, Pt 3, pp 341-345, G. Thieme Verlag, Stuttgart, 1979.

[7a] W. Bradley and K. W. Geddes, *J. Chem. Soc.*, 1630 (1952); [b] *ibid.*, 1636 (1952); [c] W. Bradley and C. S. Bruce, *ibid.*, 1894 (1954).

[8] H. D. H. Showalter, J. L. Johnson, J. M. Hoftiezer, W. R. Turner, L. M. Werbel, W. R. Leopold, J. L. Shillis, R. C. Jackson, and E. F. Elslager, *J. Med. Chem.*, in press.

[9] B. V. Ioffe, Z. I. Sergeeva, and A. P. Kochetov, *Zh. Org. Khim.*, **3**, 983 (1967); *Chem. Abstr.*, **67**, 99552z (1967).

[10] G. Gever, *J. Am. Chem. Soc.*, **76**, 1283 (1954).

[11] K. Freudenberg and H. Hess, *Ann. Chem.*, 121 (1926).

[12a] H. Klös and H. A. Offe, British Patent 880,332 (1961); *Chem. Abstr.*, **57**, 11020a (1963); [b] J. Ropenga and S. Grudzinski, *Acta Pol. Pharm.*, **41**, 579 (1984); *Chem. Abstr.*, **103**, 53776j (1985).

[13] K. Eiter and E. Truscheit, German Patent 1108233 (1961); *Chem. Abstr.*, **56**, 14080c (1962).

[14] E. F. Elslager, E. A. Weinstein, and D. F. Worth, *J. Med. Chem.*, **7**, 493 (1964).

[15] G. Gever, German Patent 1,126,877 (1962); *Chem. Abstr.*, **58**, 4579b (1964).

[16] M. Grelet, United States Patent 3,703,533 (1972); *Chem. Abstr.*, **72**, 122929s (1970).

[17] H. D. H. Showalter, J. L. Johnson, E. M. Berman, J. L. Atwood, and W. E. Hunter, *Tetrahedron Letters*, **26**, 157 (1985).

[18] H.-S. Bien, W. Hohmann, and H. Vollmann, U. S. Patent 3,631,074 (1971); *Chem. Abstr.*, **76**, 142404c (1972).

[19] C. A. Grob, *Angew. Chem., Int. Ed. Engl.*, **8**, 535 (1969).

[20] A. M. Galushko and N. S. Dokunikhin, *Khim. Geterotsikl. Soedin.*, 956 (1977); *Chem. Abstr.*, **87**, 184421p (1977).