solution; they could be extracted with Claisen's alkali.[20] This was not attempted with IVd.

5 6,7,8-Tetrahydro-5-(*p*-hydroxybenzyl)-2-naphthol Diacetate (VIIIe). General Method for VIIIa–h and Va–d.—To a 10-g sample of VIIe dissolved in 170 ml of pyridine in a stoppered 500-ml flask was added, dropwise with swirling, 40 ml of Ac_2O. This solution was swirled for 10 min at room temperature and allowed to stand overnight. H_2O (50 ml) was added dropwise to the swirled solution over a 15-min period with slight cooling in an ice bath. Further dilution gave an oil that was extracted (Et_2O). The ether extract was washed (5% HCl, H_2O, 5% Na_2CO_3, H_2O). After drying ($MgSO_4$), the solvent was removed at reduced pressure to leave an oil which crystallized from benzene–hexane to give 12.4 g of white crystals, mp 89–92°, ν_{max} 1745 cm^{-1}.

In the preparation of VIIIg, benzoyl chloride was substituted for Ac_2O and work-up was *via* $CHCl_3$ extraction. This product, 5,6,7,8-tetrahydro-5-(*p*-hydroxybenzyl)-2-naphthol dibenzoate, showed ν_{max} 1725 cm^{-1}.

6-Acetoxy-1-tetralone.—Demethylation of 6-methoxy-1-tetralone by the method described for the preparation of IVd and VIIc (including separation from neutral material by extraction of the product from ether with 10% aqueous NaOH) provided a crude pink solid: mp 127–135° (lit.[21] mp 121.0–121.5°); ν_{max} 3580, 3250 (broad), 1658 cm^{-1}. This solid resisted purification. It was acetylated by the method described for the preparation of VIIIe to give a 56% yield (from 6-methoxy-1-tetralone) of 6-acetoxy-1-tetralone as a colorless oil: bp 126–143° (0.16–0.17 mm) [lit.[21] 152–154° (1 mm)]; ν_{max} 1675, 1754 cm^{-1}. Attempted crystallization failed; lit.[21] mp 62.5°, polymorph mp 42°.

5-(*p*-Benzyloxybenzyl)-7,8-dihydro-2-naphthol Acetate and 5-(*p*-Benzyloxybenzylidene)-5,6,7,8-tetrahydro-2-naphthol Acetate (IIIh).—The Grignard reagent (56 mmoles), prepared from *p*-benzyloxybenzyl chloride in the manner described above for IIIf, was added over a period of 1 hr and 10 min to a solution of 10 g (49 mmoles) of 6-acetoxy-1-tetralone in 100 ml of dry THF cooled in an ice–salt bath. The mixture was allowed to come to room temperature overnight with stirring under N_2. At this point a negative Gilman test[22] was obtained. Work-up with ice and aqueous NH_4Cl gave about 23 g of an oil. An ir spectrum indicated the presence of some 6-acetoxy-1-tetralone. The oil was dissolved in 500 ml of toluene with 20 mg of *p*-toluenesulfonic acid and the solution was heated under reflux (Dean–Stark trap) for 1 hr. The toluene was removed at reduced pressure and replaced with ether. This solution was washed with $NaHCO_3$ and water, dried, and evaporated *in vacuo* to give about 20 g of a dark oil which could not be crystallized.

This oil was dissolved in 100 ml of 95% EtOH containing 5.5 g of KOH and this solution was heated under reflux for 1 hr, poured into H_2O (500 ml), and extracted (Et_2O) (an emulsion required that the mixture be centrifuged to effect separation of the layers). The ether extract was then extracted with Claisen's alkali,[20] washed well with water, and dried ($MgSO_4$). Removal of the solvent at reduced pressure left 7 g of a semisolid yellow-orange residue. The nmr and ir spectra of this material suggest that it is a mixture of benzyl *p*-tolyl ether and possibly *p*-benzyloxybenzyl alcohol. Work-up of the aqueous KOH solution by acidification with 10% HCl and ether extraction yielded 3.8 g of a dark red oil that partially solidified on standing but which could not be purified. Any 6-hydroxy-1-tetralone would be expected to be in this residue.

The Claisen's alkali extract upon similar work-up gave 5 g of a yellow-red oil that could not be induced to crystallize. Acetylation of this oil by the method described for the preparation of VIIIe provided 2.87 g of IIIh which separated from benzene–hexane as a near white powder, mp 85–92°, ν_{max} 1748 cm^{-1}.

6-Methoxy-1-(*p*-methoxybenzyl)naphthalene (IX).—An intimate mixture of 2 g of IIIe and 548 mg of sublimed sulfur was heated under N_2 at 205–210° for 5 hr. The mixture was cooled, taken up in ether, and filtered with slight suction. The filtrate was dried ($MgSO_4$) and the solvent was removed *in vacuo*. The residue was decolorized with charcoal in EtOH giving, after two recrystallizations, 666 mg (34%) of white crystals: mp 97–100°; λ_{max}^{EtOH} 331 mμ (ε 2570), 316 (1960), 296 (6160), 277 (7520), 231 (56,400). The nmr spectrum has a CH_2 singlet at 258 cps. *Anal.* ($C_{19}H_{18}O_2$) C, H.

5-(*p*-Hydroxybenzyl)-2-naphthol (X) was prepared from IX by the pyridine hydrochloride method described for the preparation of VIIe. A 40% yield of X was obtained as a near-white solid from Me_2CO–H_2O; mp 191–194° (after drying *in vacuo* to remove acetone). *Anal.* ($C_{17}H_{14}O_2$) C, H.

5-(*p*-Hydroxybenzyl)-2-naphthol Diacetate (XI).—Acetylation of X in the manner described for the preparation of VIIIe gave an 81% yield of XI as fine pale yellow crystals from benzene–hexane; mp 119.5–120.5°, ν_{max} 1753 cm^{-1}. *Anal.* ($C_{21}H_{18}O_4$) C, H.

Acknowledgment.—The authors are indebted to Drs. R. E. Mauer, A. I. Cohen, and R. Oslapas for biological data and wish to thank Dr. Paul Kurath for helpful advice.

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Potential Antitumor Agents. VI. Bisquaternary Salts

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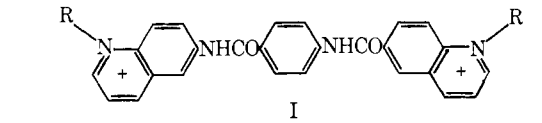
Received July 12, 1967

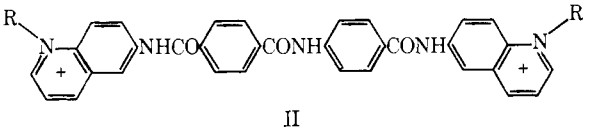
Investigations of the structure–activity relationships of a series of bisquaternary ammonium heterocycles against the L1210 leukemia system are described.

In an attempt to delineate further the features essential for experimental antileukemic activity in this area the quaternary salts represented by I were prepared. These differed from our parent series, the quaternary salts of N,N′-(6-quinolyl)terephthalamide, in the reversal of an amide function. This series (I) covering a range of lipophilic-hydrophilic properties had no active members.

Previous work[2] had shown an enhancement of experimental antileukemic effectiveness when intercharge separation was increased by a variety of means, provided



I



II

(1) Author to whom inquiries should be addressed.

(2) Part V: G. J. Atwell and B. F. Cain, *J. Med. Chem.*, **10**, 706 (1967)

Table I

Derivatives of Quinoline

Substituent	Mp, °C	Formula	Analyses
6-(*p*-Benzyloxycarbonylbenzamido)-	207–208	$C_{24}H_{18}N_2O_3$	C, H, N
6-(*p*-Carboxybenzamido)-	317–318	$C_{17}H_{12}N_2O_3$	C, H, N
6-(*p*-Methoxycarbonylphenylcarbamoyl)-	218–219	$C_{18}H_{14}N_2O_3$	C, H, N
6-(*p*-Carboxyphenylcarbamoyl)-	295–296	$C_{17}H_{12}N_2O_3$	C, H, N
6-(*p*-Nitrophenylcarbamoyl)-	228–228.5	$C_{16}H_{11}N_3O_3$	C, H, N
6-(*p*-Aminophenylcarbamoyl)-	217–218	$C_{16}H_{13}N_3O$	C, H, N

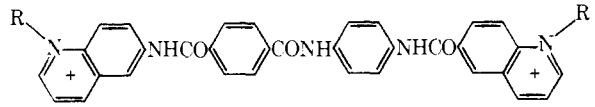
Table II

Derivatives of Pyridine

Substituent	Mp, °C	Formula	Analyses
3-[*p*-(*p*-Nitrobenzamido)phenyl]-	257.5–258	$C_{18}H_{13}N_3O_3$	C, H, N
3-[*p*-(*p*-Aminobenzamido)phenyl]-	235–236	$C_{18}H_{15}N_3O \cdot H_2O$	C, H, N
3-(*p*-Benzyloxycarbonylbenzamido)-	193–194	$C_{26}H_{20}N_2O_4$	C, H, N
3-(*p*-Carboxybenzamido)-	330–331	$C_{19}H_{14}N_2O_3$	C, H, N
3-(*p*-Nitrobenzamido)-	255–255.5	$C_{12}H_9N_3O_3$	C, H, N
3-(*p*-Aminobenzamido)-	210–211	$C_{12}H_{11}N_3O$	C, H, N
4-(*p*-Nitrobenzamido)-	245–247	$C_{12}H_9N_3O_3$	C, H, N
4-(*p*-Aminobenzamido)-	257–258	$C_{12}H_{11}N_3O$	C, H, N
3-(*p*-Methoxycarbonylbenzamido)-	165.5–166	$C_{14}H_{12}N_2O_4$	C, H, N
3-(*p*-Carboxybenzamido)-	296–297	$C_{13}H_{10}N_2O_4$	C, H, N
3-(*p*-Methoxycarbonylphenylcarbamoyl)-	197–198	$C_{14}H_{12}N_2O_4$	C, H, N
3-(*p*-Carboxyphenylcarbamoyl)-	308–309	$C_{13}H_{10}N_2O_4$	C, H, N
3-(*p*-Nitrophenylcarbamoyl)-	259.5–260	$C_{12}H_9N_3O_3$	C, H, N
3-(*p*-Aminophenylcarbamoyl)-	186–187	$C_{12}H_{11}N_3O$	C, H, N

the lipophilic–hydrophilic balance was maintained in the correct range. Extension of the intercharge separation in another manner, by the introduction of an additional *p*-aminobenzoate unit into the parent series, led to type II compounds. Due to the balance of lipophilic–hydrophilic properties of the benzenoid ring and the amide group, the physical properties of the resultant molecule still lie within the allowable partition range.[2] The effectiveness of the increased charge separation is seen in the peak member of series II (that with R = C_2H_5) which had greater activity against the L1210 system than any member of the parent N,N′-(6-quinolyl)terephthalamide series.

On the other hand reversal of one of the existing amide functions in type II (to give type III) afforded only weakly active compounds, while reversal of two amide[3] functions resulted in the completely inactive series IV.[3] Further increase in intercharge separations



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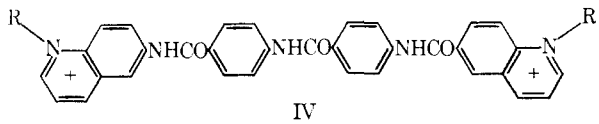
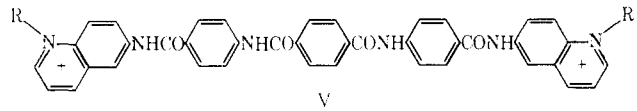


IV

by intercalation of an additional *p*-aminobenzoate unit to give V abolished activity. However, inactivity of this compound could be due to extreme insolubility in aqueous media. Also inactive was series VI in which the previously described[2] 3-phenylpyridine system was extended by intercalation of a *p*-aminobenzoate unit.

It was suggested in our earlier paper[2] that a close approach to over-all planarity could be a requirement for high activity in these quaternary salts. This

(3) The stereochemical implications of these results will be elaborated more fully in a later paper.



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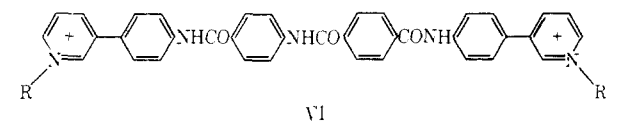
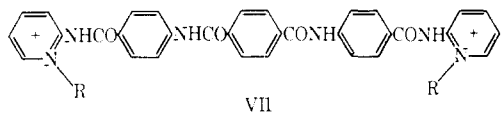


VI

prompted an examination of the acylaminopyridines in place of the more difficultly accessible phenylpyridines. While the isomeric 2- and 4-acylaminopyridine series (VII and VIII) were inactive, the 3-substituted derivatives (IX) were markedly active. In contrast to the



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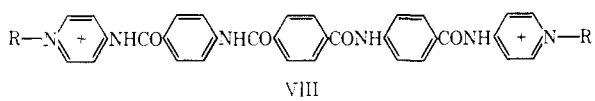
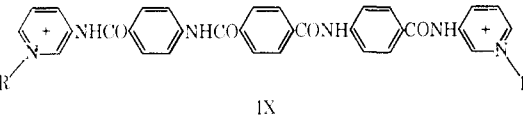
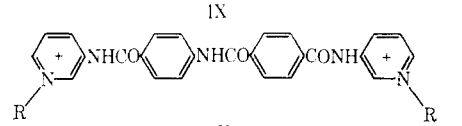


VIII



IX



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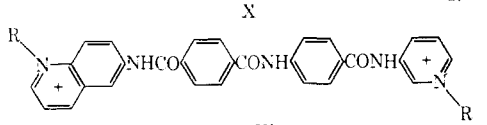
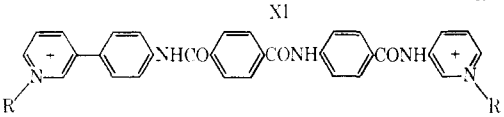


XI



XII

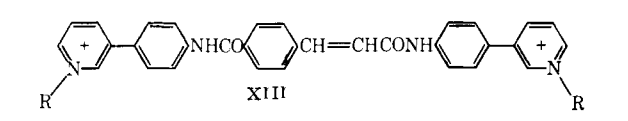
TABLE III

Compd	R	Mp, °C	Formula	Analyses	L1210[c]	R_D[d]
I	*a*	328–330	$C_{26}H_{18}N_4O_2$	C, H, N		
I	C_2H_5[b]	260–262	$C_{44}H_{42}N_4O_8S_2$	C, H, S	−	0.83
I	$CH_3(CH_2)_3$	269–271	$C_{48}H_{50}N_4O_8S_2 \cdot H_2O$	H, S; C[e]	−	0.93
I	$CH_3(CH_2)_5$	236–237	$C_{52}H_{58}N_4O_8S_2$	C, H, S	−	1.08
II	*a*	358–359	$C_{33}H_{23}N_5O_3$	C, H, N		
II	CH_3	359–360	$C_{40}H_{43}N_3O_9S_2$	C, H, N, S	+	0.65
II	C_2H_5	285–287	$C_{51}H_{47}N_5O_9S_2 \cdot 2.5H_2O$	C, H, S	++	0.81
II	$CH_3(CH_2)_2$	290–292	$C_{53}H_{51}N_5O_9S_2 \cdot 0.5H_2O$	C, H, S	+	0.91
II	$CH_3(CH_2)_3$	277–278	$C_{55}H_{55}N_5O_9S_2 \cdot 2.5H_2O$	C, H, S	+	0.96
III	*a*	>360	$C_{33}H_{23}N_5O_3$	C, H, N		
III	CH_3	308–310	$C_{49}H_{43}N_5O_9S_2 \cdot 1.5H_2O$	C, H, S	±	0.63
III	C_2H_5	225–226	$C_{51}H_{47}N_5O_9S_2 \cdot H_2O$	C, H, S	+	0.79
III	$CH_3(CH_2)_2$	231–233	$C_{53}H_{51}N_5O_9S_2 \cdot 0.5H_2O$	C, H, S	±	0.91
IV	*a*	>360	$C_{33}H_{23}N_5O_3$	C, H, N		
IV	CH_3	334–335	$C_{49}H_{43}N_5O_9S_2$	C, H, S	−	0.73
IV	C_2H_5	253–255	$C_{51}H_{47}N_5O_9S_2 \cdot 2H_2O$	C, H, S	−	0.89
IV	$CH_3(CH_2)_2$	261–263	$C_{53}H_{51}N_5O_9S_2 \cdot H_2O$	C, H, S	−	0.99
V	*a*	>360	$C_{40}H_{28}N_6O_4$	C, H, N		
V	CH_3	>360	$C_{56}H_{48}N_6O_{10}S_2 \cdot H_2O$	C, H, S	−	0.92
VI	*a*	>360	$C_{37}H_{27}N_5O_3$	C, H, N		
VI	CH_3	344–345	$C_{53}H_{47}N_5O_9S_2 \cdot 1.5H_2O$	C, H, S	−	0.93
VII	*a*	>360	$C_{32}H_{24}N_6O_4$	C, H, N		
VII	CH_3	301–303	$C_{48}H_{44}N_6O_{10}S_2 \cdot H_2O$	C, H, S	−	0.85
VII	C_2H_5	301–302	$C_{50}H_{48}N_6O_{10}S_2 \cdot 2H_2O$	C, H, S	−	0.98
VII	$CH_3(CH_2)_2$	306–307	$C_{52}H_{52}N_6O_{10}S_2 \cdot 2H_2O$	C, H, S	−	1.02
VIII	*a*	>360	$C_{32}H_{24}N_6O_4$	C, H, N		
VIII	CH_3	354–355	$C_{48}H_{44}N_6O_{10}S_2 \cdot 0.5H_2O$	C, H, S	−	0.83
VIII	C_2H_5	326–327	$C_{50}H_{48}N_6O_{10}S_2 \cdot H_2O$	C, H, S	−	0.99
IX	*a*	>360	$C_{32}H_{24}N_6O_4$	C, H, N		
IX	CH_3	336–338	$C_{48}H_{44}N_6O_{10}S_2 \cdot 3H_2O$	C, H, S	++	0.68
IX	C_2H_5	307–308	$C_{50}H_{48}N_6O_{10}S_2 \cdot 3H_2O$	C, H, S	++	0.84
IX	$CH_3(CH_2)_2$	310–311	$C_{52}H_{52}N_6O_{10}S_2$	C, H, S	++	0.94
IX	$CH_3(CH_2)_3$	309–310	$C_{54}H_{56}N_6O_{10}S_2 \cdot 1.5H_2O$	C, H, S	±	0.97
X	*a*	357–358	$C_{25}H_{19}N_5O_3$	C, H, N		
X	CH_3	280–282	$C_{41}H_{39}N_5O_9S_2$	C, H, S	−	0.83
X	C_2H_5	248–249	$C_{43}H_{43}N_5O_9S_2 \cdot H_2O$	C, H, S	−	0.91
X	$CH_3(CH_2)_2$	256–258	$C_{45}H_{47}N_5O_9S_2 \cdot 2H_2O$	C, H, S	−	1.04
XI	*a*	348–349	$C_{29}H_{21}N_5O_3$	C, H, N		
XI	CH_3	298–299	$C_{45}H_{41}N_5O_9S_2 \cdot H_2O$	C, H, S	++	0.66
XI	C_2H_5	262–263	$C_{47}H_{45}N_5O_9S_2 \cdot 0.5H_2O$	C, H, S	++	0.82
XI	$CH_3(CH_2)_2$	254–256	$C_{49}H_{49}N_5O_9S_2 \cdot 0.5H_2O$	C, H, S	++	0.93
XI	$CH_3(CH_2)_3$	230–232	$C_{35}H_{39}I_2N_5O_3 \cdot 2.5H_2O$	C, H, I	+	0.98
XII	*a*	>360	$C_{31}H_{23}N_5O_3$	C, H, N		
XII	CH_3	303–304	$C_{47}H_{43}N_5O_9S_2 \cdot 3H_2O$	C, H, S	++	0.77
XIII	*a*	>360	$C_{32}H_{24}N_4O_2$	C, H, N		
XIII	CH_3	338–340	$C_{48}H_{44}N_4O_8S_2$	C, H, S	++	0.69
XIII	C_2H_5	325–327	$C_{50}H_{48}N_4O_8S_2 \cdot 2H_2O$	C, H; S[f]	++	0.81
XIII	$CH_3(CH_2)_2$	308–309	$C_{52}H_{52}N_4O_8S_2 \cdot H_2O$	C, H, S	++	0.91
XIV	*a*	>360	$C_{34}H_{26}N_6O_4$	C, H, N		
XIV	CH_3	341–342	$C_{50}H_{46}N_6O_{10}S_2$	C, H, S	++	0.47
XIV	C_2H_5	330–332	$C_{52}H_{50}N_6O_{10}S_2$	C, H, S	++	0.65
XIV	$CH_3(CH_2)_2$	307–309	$C_{54}H_{54}N_6O_{10}S_2$	C, H, S	++	0.86
XIV	$CH_3(CH_2)_3$	310–312	$C_{56}H_{58}N_6O_{10}S_2$	C, H, S	+	0.94

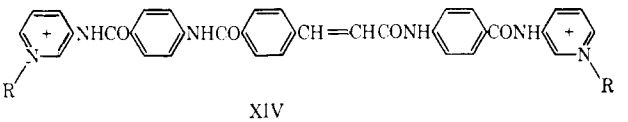
[a] Free base. [b] Common anion throughout this paper, unless otherwise indicated, is *p*-toluenesulfonate. [c] Results according to our experimental L1210 system. Increase of life span 25–50%, ±; 50–100%, +; >100%, ++. See Experimental Section for full details. [d] R_f value relative to an internal standard (Dimidium); see ref 2. [e] C: calcd, 64.6; found, 64.1. [f] S: calcd, 6.9; found, 6.4.

N,N′-(6-quinolyl)terephthalamide series the 3-acylaminopyridine (X) with similar intercharge separation is completely inactive. It is interesting that the intercharge separation in X corresponds to that in the very active 4′,4″-(di-2-imidazolinyl)terephthalanilide described by Hirt and Berchtold[4] (19.5–20 Å, variations being due to the various conformations possible about the amide functions). However, the hybrid species XI and XII contain very active members.

Using a *p*-carboxycinnamoyl function in place of a terephthaloyl group, a means of increasing charge separation described in an earlier paper has given rise to the further highly active series XIII and XIV.



XIII



XIV

(4) R. Hirt and R. Berchtold, *Experientia*, **17**, 418 (1961).

Table IV

Compd	R	Dose, mg/kg/day	Wt change	Survivors	Av survival, days		T/C, %
					Treated	Control	
II	CH_3	150		2			
		100	−0.1	6	13.9	9.9	140
		67	+1.3	6	18.0	9.9	182
		44	+2.3	6	12.8	9.9	129
		30	+1.7	6	11.9	9.8	121
	C_2H_5	40	−2.7	6	15.2	9.0	169
		27	−2.1	6	19.2	9.0	213
		18	+0.5	6	14.8	9.0	164
		12	+1.2	6	12.8	9.0	142
		8	+2.3	6	11.2	9.0	124
	$CH_3(CH_2)_2$	100	−0.9	5	17.2	9.4	183
		67	−0.5	6	16.6	9.6	173
		44	+0.5	6	13.6	9.6	142
		30	+1.1	6	11.8	9.6	123
	$CH_3(CH_2)_3$	150		3			
		100	−2.7	6	14.8	9.6	154
		67	−1.7	6	14.6	9.6	152
		44	−0.5	6	13.0	9.6	136
		30	+1.1	6	11.6	9.6	121
III	CH_3	100	0.0	5	11.5	10.8	
		67	+2.8	6	12.6	9.6	132
		44	+4.1	6	11.7	9.6	122
	C_2H_5	67	−2.8	5	11.8	9.6	123
		44	−1.2	6	15.4	9.6	160
		30	+1.3	6	11.9	9.6	124
	$CH_3(CH_2)_2$	100	−1.7	6	11.6	9.4	123
		67	−0.8	6	13.0	9.4	138
		44	+1.2	6	9.8	9.4	
IX	CH_3	60	−0.7	5	21.0	9.6	218
		40	+0.2	6	22.0	9.6	228
		27	+0.7	6	18.8	9.6	196
		18	+0.7	6	15.8	9.6	164
		12	+1.4	6	16.2	9.6	169
		8	+2.2	6	16.1	10.3	156
		5	+2.9	6	12.2	10.3	
	C_2H_5	20	−1.8	6	10.0	9.5	
		15	−0.5	6	30.7	9.5	322
		10	+1.0	6	28.6	9.5	301
		6.7	+1.7	6	45.0	9.5	474
		4.4	+2.1	6	14.2	9.5	151
		3.0	+3.7	6	12.2	9.5	128
	$CH_3(CH_2)_2$	60	−2.8	5	14.3	9.9	144
		40	+0.4	6	15.2	9.5	160
		27	+1.2	6	20.5	9.5	216
		18	+1.8	6	16.2	9.5	170
		12	+1.9	6	13.3	9.9	134
	$CH_3(CH_2)_3$	60	−7.5	5	13.0	9.5	137
		40	−1.8	6	14.2	9.5	150
		27	−0.5	6	13.2	9.5	139
		18	+3.0	6	11.0	9.5	
XI	CH_3	40	−2.4	5	14.2	9.9	144
		27	−1.2	6	20.4	9.9	206
		18	−0.2	6	18.4	9.9	186
		12	+1.3	6	14.1	9.9	143
		8	+2.3	6	12.0	9.9	121
	C_2H_5	15		1			
		10	+0.4	6	26.2	9.9	265
		6.7	+1.1	6	24.5	9.9	247
		4.4	+2.7	6	20.0	9.9	202
		3.0	+0.7	6	16.0	9.9	162
		2.0	+2.7	6	12.7	9.9	129
	$CH_3(CH_2)_2$	30		0			
		20	−2.5	6	25.5	9.9	258
		15	−0.5	6	16.9	8.9	190
		10	+0.4	6	13.8	9.7	142
		6.7	+1.1	6	11.3	10.1	
	$CH_3(CH_2)_3$	30	−3.9	6	16.3	9.9	165
		20	+1.3	6	12.9	9.9	131
		13	−0.5	6	11.9	10.6	

TABLE IV (*Continued*)

Compd	R	Dose, mg/kg/day	Wt change	Survivors	Av survival, days		T/C %
					Treated	Control	
XII	CH_3	15	−5.3	5	11.9	9.7	123
		10	+0.6	6	27.3	9.9	276
		6.7	−0.7	6	23.9	9.7	247
		4.4	+1.1	6	17.2	9.7	178
		3.0	+1.7	6	14.6	9.7	151
		2.0	+3.1	6	13.2	9.7	136
XIII	CH_3	100	−2.5	6	20.8	10.8	194
		67	−0.2	6	22.2	10.8	205
		44	+0.3	6	19.6	10.8	182
		30	+0.6	6	15.8	10.8	146
		20	+1.1	6	13.9	10.8	129
	C_2H_5	100	−3.0	6	10.2	9.8	
		67	−0.8	6	21.0	9.8	214
		44	+0.1	6	26.2	9.8	267
		30	+0.3	6	22.5	9.8	230
		20	+0.6	6	16.4	9.8	168
		13	−0.8	6	12.2	9.8	124
	$CH_3(CH_2)_2$	50	−4.5	6	8.8	9.5	
		33	−2.8	6	24.4	9.5	257
		22	−0.8	6	25.8	9.5	271
		15	+0.2	6	22.1	9.7	228
		10	+0.6	6	18.1	9.7	187
		6.7	+1.0	6	13.4	9.7	138
XIV	CH_3	150	−2.4	5	14.4	9.9	146
		100	−0.9	6	19.4	9.9	196
		67	−0.3	6	19.2	9.9	189
		44	+0.1	6	18.0	9.9	182
		29	+0.4	6	16.6	9.9	168
		20	+1.2	6	13.6	9.9	135
	C_2H_5	50	−2.2	6	17.0	9.9	168
		33	−1.2	6	16.6	9.9	164
		22	+0.8	6	16.8	9.9	170
		15	+1.9	6	15.8	9.9	160
		10	+2.8	6	14.0	9.9	139
	$CH_3(CH_2)_2$	60	−3.0	4	7.3	9.9	
		40	−1.8	6	15.3	9.9	155
		27	−0.9	6	16.6	9.9	168
		18	−0.2	6	15.5	9.9	156
		12	+0.9	6	13.7	9.9	139
	$CH_3(CH_2)_3$	22		2			
		15	−3.7	6	13.9	9.8	142
		10	−1.9	6	11.6	9.8	

It is apparent from the range of compounds described, covering a relatively wide spread of intercharge separations, that there is a considerably greater allowable flexibility in structure consonant with high activity in these quaternary salts than in the bisimidazolines so far described.[5]

Experimental Section

Analyses by Dr. A. D. Campbell of the Microchemical Laboratory, University of Otago, Otago, New Zealand. Where analyses are indicated by symbols of the elements only, analytical results obtained for those elements were within ±0.4% of the theoretical values. Melting points have been determined on an Electrothermal melting point apparatus with the makers-supplied, stem-connected thermometer and with a 2°/min heating rate from 20° below the melting point.

Symmetrical bisbases were prepared by the acylation method.[2] Insolubility of some of the amine components, for example, 3-(*p*-aminobenzamido)pyridine in toluene, made a change of solvent necessary. Diethylene glycol dimethyl ether proved successful in such cases.

For the preparation of the unsymmetrical bisbases, stepwise synthesis was necessary. For the addition of a *p*-aminobenzoate unit, it was highly desirable to acylate methyl *p*-aminobenzoate, since the methyl *p*-acylaminobenzoates obtained were readily soluble in organic media, highly crystalline, and thus readily purified in contrast to the *p*-acylaminobenzoic acids which were very insoluble, microcrystalline, and extremely difficult to purify. Pure *p*-acylaminobenzoic acids were readily obtainable from the esters by mild alkaline hydrolysis (*vide infra*).

Rather than use protected amino functions as in peptide syntheses, a nitro group was used as a precursor of an amino group. The reduction of the nitro function was carried out with finely divided Fe in aqueous solvents. This reduction proceeded very smoothly giving high yields of aromatic amine with no detectable reduction of heterocyclic components. The method evolved was to suspend or dissolve the nitro compound in a convenient volume of 60% aqueous EtOH (or aqueous DMF if the nitro compound is very insoluble) and add Fe powder (150 g/mole of nitro group) then 20 ml/mole of a starter containing 32.5 g of $FeCl_3$ in 100 ml of H_2O. On warming, an exothermic reaction usually took place (violent with greater than molar quantities). When reaction abated, the heterogeneous mixture was refluxed vigorously until the initial orange color of the intermediate oxides changed to that of black Fe_3O_4; reduction was then complete. Concentrated NH_4OH was then added (0.3 ml/ml of $FeCl_3$ starter). The solution was filtered hot, the iron oxide mixture was washed well with a suitable solvent, and the filtrate was processed for the aromatic amine. In the reduction

(5) (a) R. Hirt, Chemotherapy of Cancer, Proceedings of an International Symposium, Lugano, 1964, P. A. Plattner, Ed., Elsevier Publishing Co., New York, N. Y., 1964, p 228; J. H. Burchenal, *ibid.*, p 233; (b) L. Lee Bennett, Jr., *Progr. Exptl. Tumor Res.*, **7**, 259 (1965).

of heterocyclic bases containing a nitro function, if the pK of the starting material or the product formed on reduction was greater than 6, it was necessary to add 1 equiv of AcOH or HCl to obtain complete reduction. If, for solubility reasons, it was necessary to reduce in dilute solution, difficulty was sometimes experienced in starting the reaction. Addition of a few drops of nitrobenzene successfully initiated reduction.

Unsuccessful attempts to prepare hydrogen methyl terephthalate on a large scale led us to use the monobenzyl ester for preparation of monoamides of terephthalic acid.[2] Further investigation has shown that it is possible to prepare methyl potassium terephthalate on a large scale. Dimethyl terephthalate (37.2 g) was suspended in boiling MeOH (500 ml), and a solution of KOH (11.8 g) in MeOH (150 ml) was added dropwise to the vigorously boiling suspension. When approximately half of the alkali was added, a clear solution resulted. When the addition of all the alkali was complete, refluxing was continued for a further hour. After several hours at 0°, the crystals were collected and dried. The solid was suspended in 200 ml of H_2O at 60°, the resulting solution was filtered, and a solution of 150 g of KCl in H_2O (300 ml) at 60° was added. After thorough cooling, the crystalline salt was collected, 27.5 g, mp >360°. Samples of the free acid could be obtained by acidifying a cold, aqueous solution of the salt with HOAc and crystallizing *small* quantities from boiling H_2O. It was essential to heat and cool as rapidly as possible and avoid prolonged contact with hot H_2O. Attempts to crystallize large samples in this fashion invariably gave a product highly contaminated with terephthalic acid. The mono-K salt could be used directly in phosphorazo couplings (*vide infra*) and this was the most convenient method of obtaining monoamide esters of terephthalic acid. The monoamide monomethyl esters were hydrolyzed to the free acid by warming gently with 1 N KOH in 85% aqueous MeOH until solution was complete, then leaving for 1 hr at room temperature. After addition of an equal volume of H_2O, the solution was filtered. The acid was precipitated by the addition of the required amount of acid. Construction of the amide link was conveniently performed by using the phosphorazo method.[6]

(6) "Newer Methods of Preparative Organic Chemistry," Vol. II, W. Foerst, Ed., Academic Press Inc., New York, N. Y., 1963, Chapter 2.

Using the above methods, the intermediates listed in Tables I–III, not described in the literature, were prepared.

The general conditions used for the quaternizations, paper chromatography, and other experimental methods have been described adequately.[2]

Biological Testing.—The standard test consisted of intraperitoneal inoculation of 10^5 L1210 cells into 18.5–22.5-g C_3H/DBA_2 F_1 hybrids on day 1; drug treatment was initiated 24 hr later and was continued for 5 days. Average survivals were calculated in the usual way. An attempt has been made to test all drugs from a level which is frankly toxic, giving either toxic deaths before control deaths or marked weight loss. Lower doses at 0.2 log intervals have then been tested until a nontoxic or inactive dose level has been reached.

Table IV shows the data obtained and is virtually self-explanatory. All dosage has been intraperitoneal in 0.2-ml volume, H_2O being used as medium. Groups of six animals per dose level have been used (one control group for every five tests). The weight-change column records the difference between initial weight and that at day 8 for survivors.

The number of animals surviving as long as or longer than controls are listed under survivors. Doses have been rounded off to 2 significant figures.

Compounds that have been tested under these conditions and have given no increase in life span have been classed as negative, and this is noted with the analytical data. Full details of testing of negative compounds has not been given.

No effort has been made to determine optimum dosage schedule, routes of administration, etc. Orders of activity are gauged on percentage T/C and breadth of dose range from maximum increase in life span (ILS) to that giving only 40% ILS, figures being taken from a plot of log dose/ILS.

Acknowledgments.—We are greatly indebted to Miss L. Armiger and her capable assistants for performance of the many biological tests. This work was supported by the Auckland Division, Cancer Society of New Zealand (Inc.).

Potential Antitumor Agents. VII. Bisquaternary Salts

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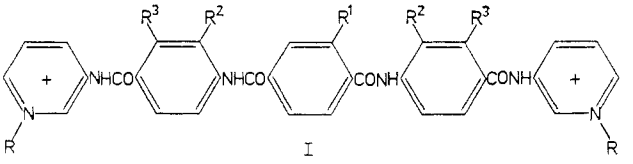
Received July 20, 1967
Revised Manuscript Received November 22, 1967

The effects of a series of substituents on the biological activity of a bisquaternary ammonium heterocycle have been determined against the L1210 leukemia system.

The last communications from this laboratory[2,3] disclosed the high experimental antileukemic activity of compound I with $R^1 = R^2 = R^3 = H$; $R = C_2H_5$.



I

While no claim is made that this compound is the most active in this series of quaternary salts, the relative ease with which the substitution pattern could be altered at will prompted a closer examination in this area. It was hoped that the results might give an insight into what would be the most rewarding area for future modifications.

Introduction of a substituent alters the lipophilic–hydrophilic balance of a species. The quaternary salts then offer a novel opportunity for examination of true structure–activity relationships since the balance of physical properties can be restored by compensatory adjustment of the quaternary function.

For preliminary investigations the substituents chlorine, methyl, methoxyl, and amino were selected, since they are relatively similar in size but cover a range of electron-donor properties. The nitro compounds required as intermediates for preparation of the amino compounds were also screened (see Table I).

Introduction of a chlorine substituent into the terephthaloyl unit gave a more lipophilic series of quaternary salts (I, $R^2 = R^3 = H$; $R^1 = Cl$) than the parent, maximum antileukemic activity being ob-

(1) Author to whom inquiries should be addressed.
(2) G. J. Atwell and B. F. Cain, *J. Med. Chem.*, **11**, 295 (1968).
(3) G. J. Atwell and B. F. Cain, *ibid.*, **10**, 706 (1967).