pound has an activation energy 1.2 kcal higher than 7-ACA. This is very close to the total observed effect. It is more likely that this is due to enhanced ability to stabilize structures such as IX. It is expected that an acetoxy methyl group will better stabilize a negative charge than will a methyl. The acetate may depart at some point as there is a measurable rate for the SN1 displacement of this group in aqueous solutions.[14] However, we find no evidence for a concerted expulsion during the enzymic reaction.

Finally, it is possible that the ring sulfur itself acts as a leaving group during the reaction, corresponding to the formation of VIII as an actual intermediate. The evidence for or against this is much less clear than in the case of acetate expulsion. There is a substantial increase of negative charge at this atom in the transition state, and the calculated bond energy of the C-S bond is nearly halved in going to the transition state. In this case solvation energies could become important. This process remains possible. However, we would expect a larger effect in the Δ^2 system because the sulfur is conjugated with a double bond. We know experimentally that the Δ^2 is stable to basic attack; yet, we find that the expulsion of sulfur is favored in this system. It is perhaps more reasonable that this process does not occur.

Conclusions

We can tentatively draw some conclusions regarding the antibacterial activity of cephalosporins and penicillins. We have considered a two-step mechanism for the inhibiting reaction: first, reversible binding of drug to the enzyme; second, irreversible formation of the covalent drug-enzyme complex. Making simple but reasonable assumptions about the nature of these steps, a clear picture of the activity of these antibiotics emerges which is consistent with experiment.

The 10- to 100-fold difference in the activity of penicillins over cephalosporins can be attributed to differential binding to the enzyme (step 1). We would expect that a cephalosporin derivative with the quasi-boat ring conformation would have considerably higher activity. There is no evidence that the presence of acetate as a leaving group plays any role in the biological activity of cephalosporins. The difference in activity between cephalosporins and desacetoxycephalosporins is well accounted for in the intact molecules. The virtual inactivity of the Δ^2-cephalosporins results from the height of the barrier to reaction with the enzyme; binding to the enzyme should be similar to that of penicillins.

The presence of sulfur as a heteroatom in the five- and six-membered ring plays a major role in the chemistry of these molecules. The size of this atom and the delocalized nature of the lone pair orbitals are important in determining the equilibrium conformation which governs binding to the enzyme. The ability to stabilize negative charge in the transition state in resonance structures such as VIII contributes to reducing the barrier to reaction with the enzyme.

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Experimental Antileukemic Agents. Coralyne, Analogs, and Related Compounds

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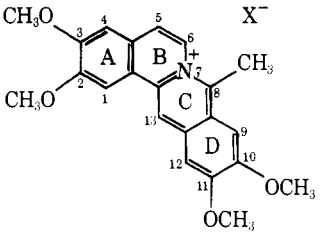
Analogs of the antileukemic alkaloid coralyne (1) and related compounds were synthesized for structure-activity study. It was found that (a) among the 8-alkyl-substituted and the 8-unsubstituted (**7g**) compounds, the 8-ethyl homolog **7d** demonstrates better antileukemic activity against leukemias L1210 and P388 in mice than the parent compound; the 8-propyl derivative **7e** is inactive, suggesting that both lipid solubility and steric effect are significant factors; (b) the planarity and rigidity of molecules of this type are critical to activity; (c) replacement of either or both *o*-dimethoxy groups of coralyne by methylenedioxy groups causes a slight decrease in the antileukemic activity; interestingly, the two bis(methylenedioxy) analogs **7c** and **7f** displayed activity in the KB cell culture system whereas the corresponding dimethoxy compounds are inactive; (d) elimination of some methoxy groups of coralyne lowers, but does not completely abolish, the original activity; and (e) activities of different salts are comparable but the acetosulfate salt is preferred because of its relatively higher solubility in water. Coralyne forms a stable complex with thymus DNA *in vitro* and exhibits reversible covalent hydration in water. The activity of coralyne against leukemia L1210 was shown to be schedule independent.

Coralyne chloride (**1a**), a hexadehydroberbinium salt, was recently found to exhibit inhibitory activity against both leukemias L1210 and P388 in mice.[1] In connection with our continued study on the structure-activity relationship of certain antileukemic agents containing the N-O-O triangular pharmacophore,[2] some analogs of cora-

lyne—including modification of the 2,3-dimethoxyl group, the 10,11-dimethoxyl group, the 8-methyl group, the planarity of dibenzoquinolizinium ring system, the chloride salt, and analogous uncyclized compounds—were synthesized in this laboratory and their antileukemic activity against both aforementioned systems was evaluated and compared.



1a, X = Cl
b, X = $C_2H_5SO_5$

Chemistry. The coralyne analogs **7a–f** were prepared in a manner similar to that used for the preparation of coralyne chloride[1] (**1a**) involving base-catalyzed condensation of the appropriate alkoxyphenethylamines **2** with alkoxyphenylacetyl chlorides **3**, cyclization of the resulting acetamides **4**, aromatization of **5**, followed by treatment of the aromatized intermediates **6** with a mixture of acid anhydride and H_2SO_4. Conversion of the acetosulfate salts of **7** to the corresponding chloride salts was readily carried out with saturated aqueous NaCl. The 8-demethylated compound **7g** (norcoralyne) was prepared from **6** (R_1, R_2, R_3, R_4 = OCH_3) by treatment of the latter with the $POCl_3$-DMF complex under the Vilsmeier-Haack conditions[3] (Scheme I).

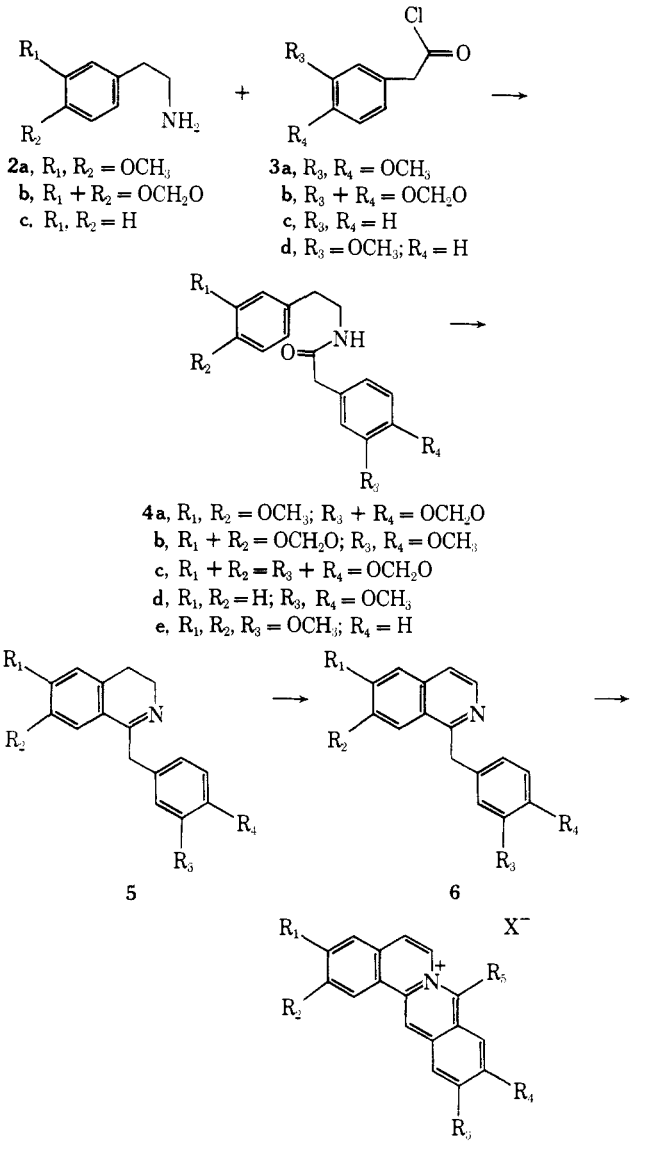
For the preparation of compound **7h**, a coralyne analog without methoxyl functions on ring A of **1**, the intermediate *N*-(2-phenethyl)-3,4-dimethoxyphenylacetamide (**4d**) was readily obtained from the amine **2c** and the acyl chloride **3a**. However, **4d** failed to cyclize to the corresponding 3,4-dihydroisoquinoline **5** under the usual Bischler-Napieralski conditions (PCl_5-$CHCl_3$). An alternative route through the isoquinoline Reissert compound[4,5] was studied. Thus, treatment of *N*-benzoyl-1-cyano-1,2-dihydroisoquinoline[5] with 3,4-dimethoxybenzyl chloride in the presence of NaH in DMF yielded compound **8**, which, upon base hydrolysis, gave the desired intermediate 1-(3,4-dimethoxybenzyl)isoquinoline (**6**, R_1, R_2 = H; R_3, R_4 = OCH_3); the latter was readily cyclized to the 2,3-didemethoxycoralyne (**7h**) *in a mixture of* Ac_2O-H_2SO_4 (Chart I).

Preparation of the coralyne analog **7i** without methoxyl functions on ring D of **1** was attempted. The key intermediate, 1-benzyl-6,7-dimethoxyisoquinoline (**6**, R_1, R_2 = OCH_3; R_3, R_4 = H), was readily prepared from **2a** and **3c** through the aforementioned general route. However, efforts to cyclize this isoquinoline by means of the Ac_2O-H_2SO_4 method were without success. Apparently cyclization reactions of this type could not take place without having some electron-donating groups substituted on the phenyl ring of the benzyl moiety. Consequently, a slightly modified structure **7j** (10-demethoxycoralyne) was chosen and this compound was prepared from **2a** and **3d** by the usual synthetic route.

Several ring-cleaved analogs of coralyne were also prepared. The acetylpapaverine **9** was obtained by treatment of coralyne **1** in strong base (at pH >13).[6] The N-alkylated papaverines **10a** and **10b** were prepared by heating papaverine (**6**, R_1, R_2, R_3, R_4 = OCH_3) with the appropriate alkyl halide in a sealed bottle.

A dihydrocoralyne analog, 5,6-dihydrocoralyne (**11**), was prepared by treatment of 3,4-dihydropapaverine (**5**, R_1, R_2, R_3, R_4 = OCH_3) with the Ac_2O-H_2SO_4 complex.

Scheme I



2a, R_1, R_2 = OCH_3
b, $R_1 + R_2 = OCH_2O$
c, R_1, R_2 = H

3a, R_3, R_4 = OCH_3
b, $R_3 + R_4 = OCH_2O$
c, R_3, R_4 = H
d, $R_3 = OCH_3$; R_4 = H

4a, R_1, R_2 = OCH_3; $R_3 + R_4 = OCH_2O$
b, $R_1 + R_2 = OCH_2O$; R_3, R_4 = OCH_3
c, $R_1 + R_2 = R_3 + R_4 = OCH_2O$
d, R_1, R_2 = H; R_3, R_4 = OCH_3
e, R_1, R_2, R_3 = OCH_3; R_4 = H

7a, $R_1 + R_2 = OCH_2O$; R_3, R_4 = OCH_3; $R_5 = CH_3$
b, R_1, R_2 = OCH_3; $R_3 + R_4 = OCH_2O$; $R_5 = CH_3$
c, $R_1 + R_2 = R_3 + R_4 = OCH_2O$; $R_5 = CH_3$
d, R_1, R_2, R_3, R_4 = OCH_3; $R_5 = CH_2CH_3$
e, R_1, R_2, R_3, R_4 = OCH_3; $R_5 = (CH_2)_2CH_3$
f, $R_1 + R_2 = R_3 + R_4 = OCH_2O$; $R_5 = CH_2CH_3$
g, R_1, R_2, R_3, R_4 = OCH_3; R_5 = H
h, R_1, R_2 = H; R_3, R_4 = OCH_3; $R_5 = CH_3$
i, R_1, R_2 = OCH_3; R_3, R_4 = H; $R_5 = CH_3$
j, R_1, R_2, R_3 = OCH_3; R_4 = H; $R_5 = CH_3$

Biological Activity and Discussion. Preliminary test results of coralyne salts, their analogs, and related compounds are listed in Table I. The antileukemic activity of coralyne is rather unique since in the leukemia P388 system, 80–100% of increase in life span of mice was observed on both daily and q4D (every 4 days) schedules.† Activity against leukemia L1210 was also noted without indication of any schedule dependency.†

A comparison of the acetosulfate salt **1b** and the chloride salt **1a** of coralyne in the P-388 and the L1210 leukemia systems indicated that both compounds are equally

†Dr. Harry B. Wood, Jr., Drug Development Branch, Drug Research and Development, Division of Cancer Treatment, National Cancer Institute, personal communication.

active when doses were freshly prepared and were given *via* the ip route. The acetosulfate salt **1b** has the advantage of being completely soluble in water—up to 14 mg/ml‡—while the chloride salt was less soluble and has a tendency to form a gel-like suspension.

The 8-ethyl homolog[6] (**7d**, X = $C_3H_5SO_5$, homocoralyne) of coralyne displayed slightly better activity against leukemia L1210 system than coralyne. This may be due to higher lipid solubility of **7d** as opposed to that of coralyne. The 8-demethylated compound (**7g**, X = Cl, norcoralyne), although having rather low solubility in water, still showed antileukemic activity in the P388 system. The steric effect seems to play an important role here since the corresponding 8-propyl homolog (**7e**, X = $C_4H_7SO_5$) was found to be totally inactive against leukemia L1210.

5,6-Dihydrocoralyne acetosulfate (**11**), papaverine (**6**, R_1, R_2, R_3, R_4 = OCH_3) hydrochloride,§ quaternary salts of papaverine methiodide (**10a**), and papaverine ethyl bromide (**10b**) do not exhibit antileukemic activity in P388 or L1210, indicating that conformational requirements, especially structural planarity, are of importance to antileukemic activity. The planar structure of these compounds, which contains the N-O-O feature, may be essential for the intercalation or interaction with the receptor biopolymers.

The effect of alkoxyl groups on the activity can be summarized as follows. Replacement of two methoxy groups at either the 2,3 or the 10,11 positions of **1** by a methylenedioxy function (compounds **7a,b**) or replacement of all four methoxy groups by two methylenedioxy functions (compound **7c**) caused a slight decrease in the original antileukemic activity and an increase in toxicity to the host. It is of interest to note that omission of some alkoxy groups in **1**, as in the case of 2,3-didemethoxy compound **7h** and the 10-demethoxy compound **7j**, did not entirely eliminate the original antileukemic activity.

It has been observed that antileukemic activity of many compounds in the coralyne series is manifested at lower dose levels. Although the mode of action and the active species of compounds of this type are not yet known, a possible explanation is that these compounds may be converted *in vivo* through hydration, hydroxylation, or other enzyme-catalyzed metabolic process to the active species. The conversion may be hindered by these same compounds at higher concentration (higher dose level) by certain feedback inhibitory mechanisms.

The acetyl derivative of papaverine, **9**, still possessed some antileukemic activity. This could well be due to its *in vivo* conversion to coralyne (it was found that acetylpapaverine gradually cyclized to coralyne in either boiling ethanol or in strongly acidic solution at room temperature) or related active species. Coralyne was found to readily react with water, forming covalent hydration products at different pH's. The equilibrium can be reversed upon lyophilization. A detailed account in this regard will be reported elsewhere.# In addition, coralyne was also noted to interact with thymus DNA *in vitro* to form a stable complex;[7] the phenomenon may be associated with its unique biological activity.

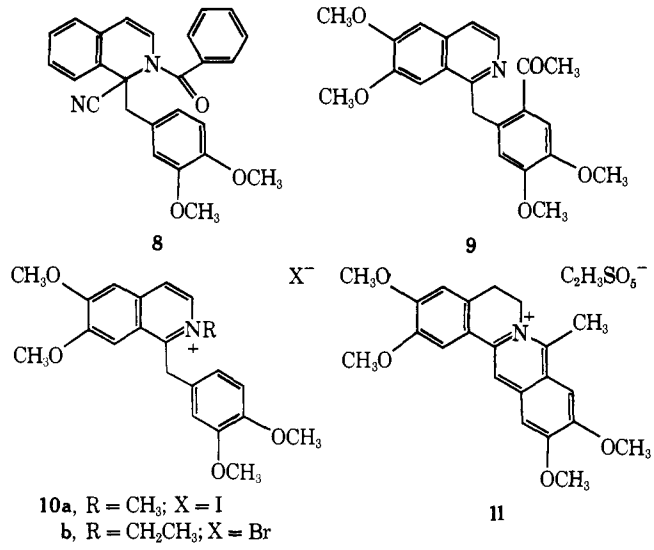
Two bis(methylenedioxy) analogs, **7c** and **7f**, demonstrated *in vitro* confirmed activity against human epidermoid carcinoma of the nasopharynx (KB).

‡Dr. Fred W. Starks, Starks Associates, Inc., personal communication.

§Papaverine hydrochloride, NSC-35443, was found to be inactive against leukemias L1210 and P1534, Dunning leukemia, Walker carcinosarcoma 256 (subcutaneous), and KB (cell culture); Dr. Harry B. Wood, Jr., National Cancer Institute, personal communication.

#M. J. Cho, I. H. Pitman, A. J. Repta, T. Higuchi, K. Y. Zee-Cheng, and C. C. Cheng, unpublished work.

Chart I



Both the acetosulfate and the chloride salts of coralyne were found to be stronger inhibitors of the enzyme catechol *O*-methyltransferase[8,9] (COMT) than pyrogallol at 0.1 m*M* concentration.

Experimental Section

Melting points were taken with a Thomas-Hoover melting point apparatus. Analytical results were obtained for C, H, and N for all compounds and were within ±0.4% of the theoretical values.

Analogs of coralyne, **7a–f**, were prepared in a manner similar to that used for the preparation of coralyne.[1] Yields and melting points are recorded in Table I. The uv absorption characteristics of these analogs are similar to those of coralyne.[1,7]

2,3,10,11-Tetramethoxydibenzo[*a,g*]quinolizinium Chloride (7g, X = Cl). To 10 ml of DMF was added dropwise, during a 5-min interval, 4 ml of distilled $POCl_3$. The resulting mixture was stirred for 15 min in an ice bath and to it was added dropwise, with stirring, a solution of 6 g (0.018 mol) of papaverine[10] (**6**, R_1, R_2, R_3, R_4 = OCH_3) in 35 ml of DMF. The mixture was stirred for 1 hr, heated on a steam bath for 2 hr, and cooled. It was then poured slowly, with stirring, into a mixture of dilute HCl and ice. The solid which separated was collected by filtration, washed successively with H_2O (2 × 80 ml), MeOH (2 × 50 ml), and Et_2O (2 × 100 ml), and dried to give 6.5 g of **7g** (X = Cl), mp 275–278°. Recrystallization from aqueous AcOH containing dilute HCl gave pure **7g** (X = Cl) as a hemihydrate, mp 298–300°. *Anal.* ($C_{21}H_{20}ClNO_4$) C, H, N. In a similar manner, recrystallization from aqueous AcOH containing dilute HNO_3 yielded the corresponding nitrate salt, mp 303–305°.

10,11-Dimethoxy-8-methyldibenzo[*a,g*]quinolizinium Acetosulfate (7h, X = $C_2H_3SO_5$). To 5 ml of Ac_2O at 0° was added, with stirring, 1 ml of concentrated H_2SO_4. The mixture was heated at 95° for 10 min. To the resulting wine-colored mixture was added, with cooling, 1.1 g (0.0035 mol) of 1-(3,4-dimethoxybenzyl)-isoquinoline hydrochloride.[5] The solution was heated at 95–100° for 50 min. It was then cooled and diluted with 2 ml of EtOH and 30 ml of Et_2O. The mixture was cooled at 0° overnight. The solid was collected by filtration, washed with Et_2O (2 × 20 ml), and dried to give 1.8 g of **7h** (X = $C_2H_3SO_5$), mp 220–225° dec. An analytical sample was prepared by recrystallization from MeOH–Et_2O and obtained as light yellow crystals, mp 238–240° dec. *Anal.* ($C_{22}H_{21}NSO_7$) C, H, N.

6,7-Dimethoxy-1-(3,4-dimethoxybenzyl)-2-ethylisoquinoline Bromide (10b). A mixture of 5.1 g (0.015 mol) of papavarine and 10 ml of EtBr in 15 ml of $CHCl_3$ was heated on a steam bath in a sealed bottle for 7 hr. The mixture was cooled and to it was added 60 ml of Et_2O. The resulting precipitate was collected by filtration, washed with Et_2O, and dried to give 5.9 g of **10b**, mp 165–168° dec. Recrystallization from EtOH–Et_2O gave mp 165–167° dec. *Anal.* ($C_{22}H_{26}BrO_4$) C, H, N.

6,7-Dimethoxy-1-(3,4-dimethoxybenzyl)-2-methylisoquinoline iodide (10a), mp 158–160° dec, was prepared from papaver-

Table I. Coralyne Salts, Analogs, and Related Compounds[a]

Compd	Formula	Mp, °C (recrystn solvent)	Yield, %	Antileukemic activity: P388 Dose, mg/kg	P388 Survival	P388 Wt diff	P388 T/C, %	L1210 Dose, mg/kg	L1210 Survival	L1210 Wt diff	L1210 T/C, %
1a	$C_{22}H_{22}ClNO_4 \cdot 0.5H_2O$	250–252 dec (EtOH)	100	400	73/74	−1.7	167	400	6/6	−3.2	139
				300	29/30	−1.1	181	200	32/32	−1.2	136
				200	71/72	−1.9	181[b]	100	6/6	−1.7	134
				100	89/90	−1.9	167				
				50	42/42	−1.5	169				
				25	18/18	−0.7	153				
1b[c]	$C_{24}H_{25}NO_9S$	278–280 dec (MeOH)	83	400	6/6	−3.8	195	400	14/14	−4.8	109
				300	10/10	−2.2	193	256	24/30	−2.8	130
				200	17/18	−3.7	179	200	55/55	−3.5	130
				160	11/12	−2.0	163	100	65/65	−2.5	126
				100	12/12	−2.2	166	64	79/80	−1.4	125
								50	12/12	−1.3	124
				75	19/20	−1.4	169				
				40	12/12	−1.0	166				
				20	18/18	−0.0	165				
				5	18/18	+0.3	157				
7a (X = $C_2H_3SO_5$)	$C_{23}H_{21}NO_9S$	277–279 dec (MeOH)	79					400	0/6		
								200	1/6		
								100	10/12	−3.0	105
								50	6/6	−1.7	122
								25	12/12	−1.2	134
								11	6/6	−0.0	107
7b[d] (X = $C_2H_3SO_5$)	$C_{23}H_{21}NO_9S$	293–295 dec (MeOH)	45					400	2/6		
								200	11/12	−1.5	93
								100	12/12	−1.3	121
								50	6/6	−2.6	102
								25	6/6	−1.6	144
								12	6/6	−1.3	133
7c[e] (X = $C_2H_3SO_5$)	$C_{22}H_{17}NO_9S$	305 dec (MeOH)	48	25	6/6	−2.2	95	400	0/6		
				18.7	12/12	−1.8	125	200	1/6		
				12.5	18/18	−1.8	173[f]	100	6/6	−2.4	70
				8.33	12/12	−2.1	186	25	6/6	−2.3	90
				6.25	6/6	−1.2	170	12.5	6/6	−1.8	129
				5.56	12/12	−1.5	163	8.3	6/6	−1.4	128
								6.2	6/6	−0.0	116
7d[g] (X = $C_3H_5SO_5$)	$C_{26}H_{29}NO_9S \cdot H_2O$	292–293 dec (MeOH)	79	200	6/6	+0.5	181	400	6/6	−3.3	121
				100	12/12	−2.2	219[h]	300	10/12	−1.9	127
				50	5/6	−2.2	215	200	18/18	−3.0	136
								150	6/6	−3.6	156
								100	6/6	−3.2	142
								66	6/6	−3.1	150
								44	6/6	−3.4	147
7e[i] (X = $C_4H_7SO_5$)	$C_{28}H_{33}NO_9S$	254–256 dec (EtOH)	68					400	3/6		
								200	6/6	+0.6	110
								100	6/6	−1.2	100
7f[j] (X = $C_3H_5SO_5$)	$C_{24}H_{21}NO_9S$	320–322 dec (MeOH–Et_2O)	26					200	0/6		
								100	1/6		
								50	2/6		
								25	6/6	+0.5	72
								12.5	12/12	−1.5	114
								6.25	11/12	−1.8	110
								3.13	12/12	−1.0	118
7g[k] (X = Cl)	$C_{21}H_{20}ClNO_4 \cdot 0.5H_2O$	298–300 dec (HOAc–H_2O–HCl)	92	320	6/6	−1.3	77	320	6/6	−3.0	93
				160	12/12	−1.3	166	160	6/6	+0.2	114
				80	12/12	−0.9	154	80	6/6	−0.2	111
				40	12/12	−0.3	143	40	6/6	+0.8	119
				20	12/12	−0.1	145	20	6/6	−0.2	117
				10	6/6	+0.6	118	10	6/6	+0.2	92
				5	6/6	−0.4	109				
7h (X = $C_2H_3SO_5$)	$C_{22}H_{21}NO_7S$	238–240 dec (MeOH–Et_2O)	86	160	2/6						
				80	4/6	−4.9	59				
				40	12/12	−1.7	102				
				20	12/12	−1.9	111				
				10	12/12	−1.5	152				
				5	12/12	−1.0	147				
				2.5	6/6	+0.9	140				
7j (X = $C_2H_3SO_5$)	$C_{23}H_{23}NO_9S$	256–258 dec (MeOH)	81	400	0/6						
				200	11/12	−5.0	109				
				100	12/12	−2.9	145				
				50	18/18	−2.6	167				
				33	6/6	−2.3	186				

Table I (*Continued*)

Compd	Formula	Mp, °C (recrystn solvent)	Yield, %	Antileukemic activity: P388 Dose, mg/kg	P388 Survival	P388 Wt diff	P388 T/C, %	L1210 Dose, mg/kg	L1210 Survival	L1210 Wt diff	L1210 T/C, %
9	$C_{22}H_{23}NO_5$	140–142	83	160	6/6	−1.6	59				
				80	6/6	−1.0	90				
				40	6/6	+2.0	100				
				20	6/6	+0.5	154				
				10	6/6	−0.2	173				
				5	6/6	−0.5	127				
10a	$C_{21}H_{24}INO_4$	158–160 dec (MeOH–Et_2O)	83					400	1/6		
								200	4/6	+0.5	95
								100	6/6	+0.8	98
								50	12/12	−0.7	106
								25	6/6	+0.5	102
								12.5	6/6	−0.0	104
10b	$C_{22}H_{26}BrNO_4$	165–167 dec (EtOH–Et_2O)	89	200	0/6			200	2/6		
				100	5/6	−0.5	104	100	6/6	−0.2	98
				50	6/6	+0.7	90	50	5/6	−0.4	115
								25	6/6	−0.4	94
11	$C_{24}H_{27}NO_9S$	277–279 dec (MeOH)	68					200	0/6		
								100	10/12	−4.1	116
								50	6/6	−5.6	107
								25	5/6	−4.6	104

[a] For general screening procedure and data interpretation, *cf.* R. I. Geran, N. H. Greenberg, M. M. MacDonald, A. M. Schumacher, and B. J. Abbott, *Cancer Chemother. Rep.*, **3** (2), 1 (1972); Instruction Booklet 14, "Screening Data Summary Interpretation," Drug Research and Development, Chemotherapy, National Cancer Institute, Bethesda, Md., 1972. [b] 1–2 cures in groups of six to ten mice were occasionally observed at doses of 25–200 mg/kg. [c] 1–3 cures against B16 melanocarcinoma in groups of ten mice were noted at doses of 12.5–200 mg/kg. [d] The corresponding chloride salt was prepared in 85% yield, mp 292–294° dec. [e] Cell culture (KB): ED_{50} at 1.0×10^{-1} μg/ml. Activity confirmed. [f] One cure each in one group of six mice was observed at doses of 12.5 and 8.33 mg/kg. [g] The corresponding chloride salt was prepared in 85% yield, mp 252–254° dec. [h] Two cures in one group of six mice were observed at dose of 100 mg/kg. [i] The corresponding chloride salt was prepared in 85% yield, mp 235–237° dec. [j] Cell culture (KB): ED_{50} at 2.2×10^{-1} μg/ml. Activity confirmed. [k] The corresponding nitrate salt was prepared in 80% yield, mp 303–305° dec.

ine and CH_3I in a manner similar to that described for **10b**. *Anal.* ($C_{21}H_{24}INO_4$) C, H, N.

5,6-Dihydro-8-methyl-2,3,10,11-tetramethoxydibenzo[*a*,*g*]-quinolizinium acetosulfate (**11**), mp 277–279° dec, was prepared from dihydropapaverine (**5**, R_1, R_2, R_3, R_4 = OCH_3) in a manner similar to that used for the preparation of coralyne. Uv absorption of this compound is similar to that of dehydro-α-coralydine.[11] *Anal.* ($C_{24}H_{27}NO_9S$) C, H, N.

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9,11-Seco Steroids. An Attempt to Separate Biological Activities *via* Ring Cleavage

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A series of seco steroids with rings A and B aromatic was synthesized in order to determine the effect which scission of the 9,11 bond has on biological activities. One compound, **5a**, was found to have antiestrogen, antifertility, and antiinflammatory properties, with an estrogenic activity approximately 0.003% that of estrone.

Molecular modification has been employed as a means of enhancing specific biological activities while reducing or eliminating less desirable effects. Application of this process has led to the successful development of potent antiinflammatory steroids,[1] anabolic agents with reduced androgenic properties,[2] orally active progestins,[3] and long acting estrogens.[4]

Of the four classes of steroid hormones (corticosteroids,