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Synthesis and Antihypertensive Activity of Some Thienylethanolamines

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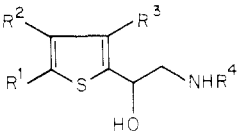
Synthesis of a series of thienylethanolamines having varying substituents on the thiophene ring and on the nitrogen atom is described using the general procedure reported earlier. In the determination of their pharmacological profile, some of the derivatives showed marked antihypertensive activity in the spontaneously hypertensive rat model. Tests are also reported which demonstrated that some of these derivatives antagonized α- and/or β-adrenoreceptor activities. The ability of this class of compounds to inhibit catecholamine-induced release of free fatty acids by adipose tissue was demonstrated. Structure–activity relationships in different tests were also determined.

The synthesis of analogues that mimic or block the effect of the adrenergic neurotransmitters represents a vast area of activity of medicinal chemists. We have reported recently[2a] the synthesis of some thiophene isosters of phenylethylamines. In this communication, we report the synthesis of some novel analogues of the same series and the biological profile of compounds of this class.

Chemistry. The thienylethanolamines of the type **1** were prepared as described[2a] starting with suitably substituted thiophenes according to the following scheme: thiophene → Friedel–Crafts type acylation → bromination of methyl ketone → reduction to alcohol → displacement of bromine by suitable amine. In our earlier work, because of the profound sympathomimetic properties of isoproterenol and sympatholytic properties of propranolol, both of which have the isopropylamine moiety as their partial structure, we chose to incorporate this amine in our analogues. In the present work, we have varied the amine moiety to explore the effect of this change on the pharmacological activity profile. The amines used for this purpose were either commercially available or synthesized by described procedures. Phenethylamine **2** was prepared by reducing the corresponding nitrile.[2b] More recently,[3] compounds having a 4-(*o*-tolyl)-1-piperazinyl group incorporated in aryloxyethylamines were reported to have vasodilator properties. Compounds **3** and **4** were therefore synthesized to investigate their cardiovascular effects.



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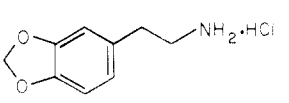

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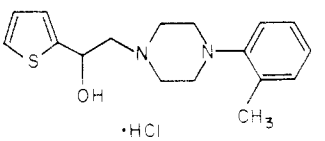

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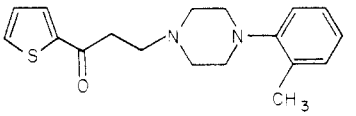

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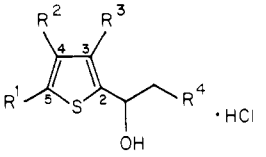
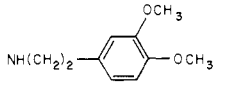
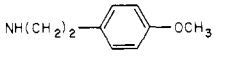
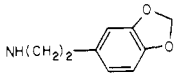
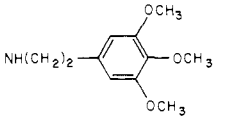
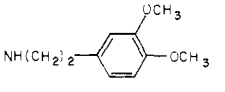
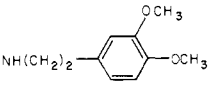
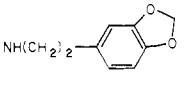
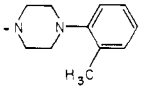
Pharmacology. Antihypertensive Activity. The blood pressure lowering property of a compound may be mediated in many different ways, e.g., (a) by direct actions on the central nervous system, via ganglionic blockade of impulses or by depletion of catecholamines from sympathetic postganglionic neurons; (b) by interfering with the adrenergic mechanisms by blocking α- or β-receptors; (c) by a direct effect on peripheral vascular smooth muscle;

Table I. Antihypertensive Activity in Spontaneously Hypertensive Rats

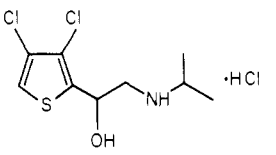


No.	R^1	R^2	R^3	R^4	Dose, mg/kg po	Fall in blood pressure[a]
5	Br	Br	H	$NHCH(CH_3)_2$	50	+++
5a	Br	H	H	$NHCH(CH_3)_2$	50	+
6	Cl	Cl	H	$NHCH(CH_3)_2$	25	++
7	Cl	Cl	H		100	+++
					25	++
8	Cl	Cl	H		50	++
					25	+
9	Cl	Cl	H		50	++++
27[b]	Cl	Cl	H		100	++++
					25	++
10[c]	CH_3	H	H		50	+++
					25	++
11	Ph	H	H		50	+
12	CH_3	H	H		50	++
					25	+
					10	+
3	H	H	H		100	++
					50	++
					25	+
4[d]					50	++++
					10	++
Clonidine					0.1	++++

[a] +, <10%; ++, 10-15%; +++, 15-20%; ++++, >20%. [b] Compounds **25** (100 mg/kg), **13** (100 mg/kg), and **26** (50 mg/kg), when given orally to spontaneously hypertensive rats, were found to have no effect on blood pressure or heart rate. [c] Tested as the oxalate salt. [d] See formula in text.

and (d) by lowering plasma volume. A compound could conceivably mediate its overall antihypertensive effect through more than one of the above pathways. In recent years β-blockers have attracted considerable attention in the therapy of hypertension. The combined therapeutic effect of a β-blocker, a peripheral vasodilator, and a diuretic offers a formula of considerable interest in certain refractory cases of hypertension, as discussed in a recent review.[19] In the present study, we first turned our attention toward the determination of the antihypertensive effect of these compounds in spontaneously hypertensive rats (SHR). The results of these tests are listed in Table I.

The variation of the substituents on the thiophene ring has a profound influence on the overall blood pressure lowering activity of the compounds. Compound **6** is isosteric with dichloroisoproterenol (DCI). DCI has well-established β-adrenergic blocking properties,[4] without an acute effect on blood pressure in the SHR model.[20] It is interesting to note that the isosteric compound **6** does have acute blood pressure lowering effects. Rotating the two chlorine atoms to positions C-3 and C-4 of thiophene as in **13**,[2a] as well as placing the ethanolamine side chain at C-3 and the two chlorine atoms at C-2 and C-5 as in compound **14**, led to a product which did not lower blood pressure. Thus, presence of substituents at C-4 and C-5 appears to be essential for the antihypertensive effect in this test.



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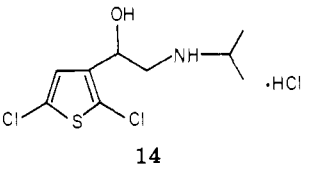

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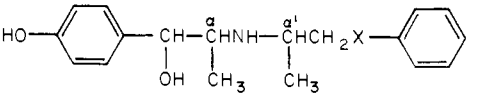
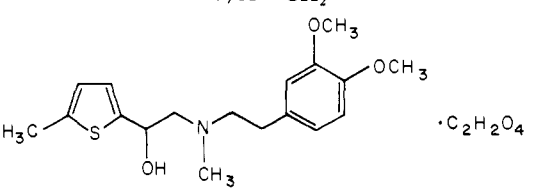
The dibromo analogue **5** also showed a blood pressure lowering effect being equipotent with its dichloro isoster **6**. Whereas the monobromo derivative **5a** still retained the antihypertensive activity, the monochloro derivative **18** was inactive. This suggests a need for a bulky substituent at either the C-4 and/or C-5 position. In the case of 4,5-dichlorothiophene, changing the isopropyl substituent to the substituted phenethyl group resulted in only small changes in the blood pressure lowering property. Thus, the methoxyphenyl compound **8** and the dimethoxyphenyl derivative **7** essentially retained the antihypertensive effect of its isopropyl analogue **6**. In contrast, replacement of the protons of the catechol group by a methylenedioxy substituent as in **9** led to a significant enhancement of antihypertensive potency.

It should be mentioned that changing the substituent at C-4 and C-5 had little influence on the blood pressure lowering effect. Thus, compounds **10** and **11**, in comparison to **7**, still retained the antihypertensive effect but to a lesser extent in the case of compound **11**.

One of the metabolic pathways of biogenic amines and their derivatives is their oxidation by monoamine oxidases to the corresponding aldehydes or ketones. Compounds such as isoxuprime[5] **15** and nylidrin[6] **16**, which are established peripheral vasodilators, have the nitrogen atom flanked on both α- and α′-carbon atoms by a methyl group. It is reasonable to assume that due to this steric crowding at α,α′ positions, the compounds may become a poor substrate for the enzyme monoamine oxidase. In a similar



15, X = O
16, X = CH_2

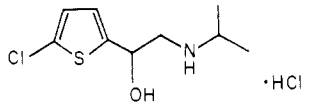


17

manner it was conceived that converting the secondary amine to a tertiary amine can also lead to a similar result. Therefore, the *N*-methyl derivative **17** of the thienylethanolamine **10** was prepared. This product has no antihypertensive effect. A need for the presence of a

proton on the nitrogen atom for biological interaction at myocardial adrenergic β-receptors has also been demonstrated in a recent report[7] on another group of myocardial β-stimulants. The ability of a 4-(*o*-tolyl)-1-piperazinyl substituent to impart antihypertensive activity was clearly demonstrated by the results in the SHR test of compound **3**. Furthermore, a 25–30 and 10–15% lowering of blood pressure was observed when compound **4** was administered orally to hypertensive rats in doses of 50 and 10 mg/kg, respectively.

Some of these compounds were selected for further studies in dogs. When anesthetized normotensive dogs were given, intravenously, compounds **7**, **9**, and **11**, these compounds partially inhibited the positive chronotropic effect of isoproterenol. However, the isoproterenol-induced blood pressure decrease was not markedly affected. In contrast, compound **5** demonstrated a myocardial β-stimulant effect. This was also indicated by tachycardia in the SHR. A similar observation of mixed myocardial β-stimulant/β-blocking properties in dogs was also noted for compounds **18**[2a,8] and **19**.



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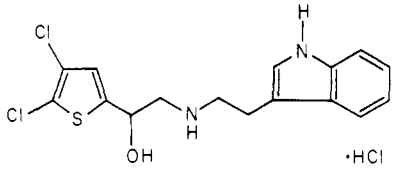

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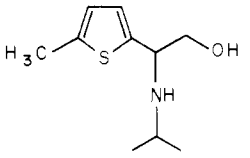

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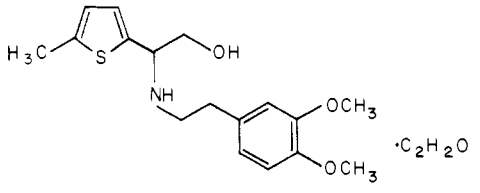

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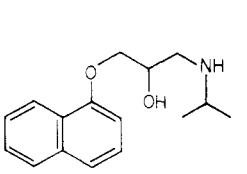
Compound **21**, which is a regioisomer of compound **10**, and its related isopropylamine analogue **20** were also tested in anesthetized normotensive dogs in this test. These were devoid of antihypertensive activity in SHR model, as well as β-blocking activities in this model.

It is well documented that β-adrenergic blockers, such as propranolol **22** and practolol **23**, do not cause hypotension when administered acutely to SHR. However, antihypertensive activity can be demonstrated in the SHR following chronic treatment.[9] Some of the thienyl compounds, e.g., **7**, **9**, and **11**, showed an acute antihypertensive effect in the SHR model, as well as a β-blocking property in dogs. The evidence is, however, insufficient to assess the contribution of β-adrenoreceptor blockade in the generation of an antihypertensive effect by these compounds.



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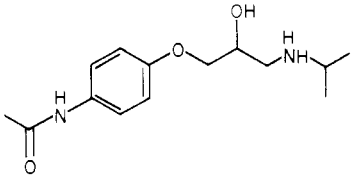

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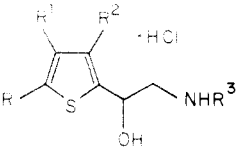
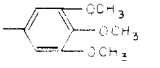
In order to obtain greater insight into the mechanism of action of this class of compounds, the following tests were performed. Selected compounds were tested in normotensive rats[10] which were challenged with various vasopressor agents whose effects are mediated by α- and/or β-adrenergic receptors. The compounds were also tested for their ability to inhibit the pressor response generated by electrical stimulation of the spinal cord.[11] The results of these tests are given in Table II.

The results reveal that, in addition to a β-blocking effect demonstrated by members of thienylethanolamine series, these compounds are capable of inhibiting pressor responses mediated via α-adrenergic receptor stimulation. Thus, the acute antihypertensive effect demonstrated by this series of compounds in the SHR model can be considered to be, at least partially, mediated via an inhibition of α-adrenergic receptors. Conversely, not all of the compounds that demonstrated an antihypertensive effect had the same degree of α-blocking capacity; e.g., compounds **12** and **4**, which demonstrate similar blood pressure lowering effects at 10 mg/kg, vary markedly in their α-adrenergic receptor blocking ability. No inhibition of blood pressure responses to angiotensin or vertical tilt were observed, even with compounds that inhibited responses of epinephrine and tyramine.

In view of the fact that some of the thienylethanolamines of the series under discussion have been shown to have β-receptor blocking properties in vivo and that β-blockers in general have been shown to inhibit norepinephrine-induced lipolysis, it was of interest to determine the ability of the present series of compounds to inhibit this hormone-induced lipolysis. The results of these experiments are shown in Table III.

Compound **6**, which is isosteric with DCI, was found to possess a high degree of activity in this assay. However, the activity of **6** was significantly less than that of DCI in the same assay. Replacement of chlorine by bromine



25, R = H; $R^1 = R^2 = Br$; $R^3 = -CH(CH_3)$
13, R = H; $R^1 = R^2 = Cl$; $R^3 = -CH(CH_3)_2$
26, R = H; $R^1 = R^2 = OCH_3$; $R^3 = -CH(CH_3)_2$
27, R = R^1 = Cl, R^2 = H; R^3 = 

atoms as in **5** appears to make little, or no, difference in the activity. Upon removal of a chlorine atom from dichloro **6** to generate monochloro **18**, the activity drops from 88 to 49% at 1×10^{-4} M, whereas similar elimination of a bromine atom from the dibromo compound **5**, leading to the monobromo compound **5a**, made little difference in activities to inhibit lipolysis in this assay. These results may imply a requirement of bulky groups at position C-4 and/or C-5 of the thienylethanolamine **29**. A shift of the substituents from positions C-4,C-5 to C-3,C-4 as in 3,4-dibromo analogue **25** and 3,4-dichloro analogue **13**[2a] resulted in a marked lowering in activity. Considering a particular conformation for the ethanolamine side chain, the C-4 and C-5 positions of the thiophene nucleus **29**

Table II. Inhibition of Pressor Responses to α-Adrenergic Stimulation

No.	Conscious rat (epinephrine, phenylephrine) Dose, mg/kg po	% inhibn	Pithed rat (spinal elec stimulation) Dose, mg/kg po	% inhibn	Recovery,[a] min
6			10	28.2	3
7			5	54.2	18
9			5	52.5	3
10			5	28.5	12
12	5 iv	42.2, 34.6, 24.1[b]	5	8.7	
24[d]	50 po	Inactive	5	33.6	15
	5 iv	43.8, 17.4, 1.8[b]			
3	100 po	56.7[c]	10	43.4	10
4	50 po	76.2[c]	5	88.7	>45
11	50 po	Inactive	5	0	
	5 iv	Inactive[b]			
Phentolamine	2.5 po	100[c]	1	72	

[a] Time of recovery of at least 90% of the lowest of three pretreatment pressor responses. [b] Inhibition of three consecutive geometrically increasing doses of phenylephrine. [c] Reversal or biphasic responses to epinephrine and tyramine.

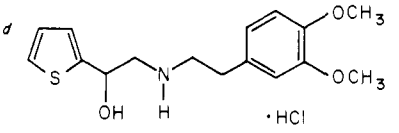


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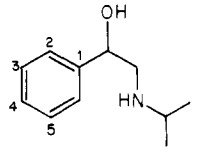
Table III. Inhibition of Norepinephrine-Induced Lipolysis

No.	% inhibn of hormone-induced lipolysis[a] 5 × 10⁻⁴ M	1 × 10⁻⁴ M	1 × 10⁻⁵ M
5	94[d]	93[d]	44[c]
5a	100[d]	90[d]	46[d]
18	100[d]	49[c]	
6	91[d]	88[c]	40[b]
25	89[d]	28	
13	67[d]	+4	
26	41[b]		
7	61[b]	13	
27	69[b]		
9	47[c]		
10	93[d]	27[b]	

[a] All values are an average of five in vitro determinations per compound. [b] $p < 0.05$. [c] $p < 0.01$. [d] $p < 0.001$ as compared with norepinephrine-induced lipolysis.



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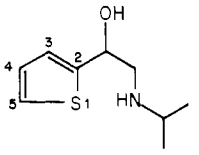

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correspond to C-3 and C-4 of the substituted phenylethanolamine **28**. Thus, the greater potency of compounds having substituents at C-4 and C-5, e.g., **5**, **5a**, **18**, and **6**, and the reduced potency by shifting the C-5 substituent to C-3, as in **25**, **13**, and **26**, can be satisfactorily accommodated by the isosteric nature of **28** and **29**. This structural requirement also became apparent in the antihypertensive assay in SHR. Replacing the *N*-isopropyl group of compound **6** by di- and trimethoxyphenylethyl, as in **7** and **27**, markedly lowered the ability of the compound to inhibit norepinephrine-induced lipolysis. In contrast, the acute antihypertensive effect in SHR is essentially unaffected by replacing the isopropyl group of compound **6** by dimethoxyphenylethyl of compound **7**. Compound **7** was shown to inhibit partially the isoproterenol-induced tachycardia in dogs, indicating that **7** can interact weakly with the myocardial β-adrenoreceptors in this model. As indicated above, **7** was also a weak antagonist in the lipolysis model. The methylenedioxy group on the phenylethyl chain further reduces activity in this assay. It is of interest to note that compound **10**, which has a dimethoxyphenethyl group on nitrogen and a methyl group at C-5, showed significant activity at a concentration of 5×10^{-4} M. However, this drops markedly at 1×10^{-4} M indicating a poor substrate–enzyme affinity relative to compounds **5** and **6**.

Table IV. Release of Norepinephrine from Mouse Heart

No.	Dose, mg/kg po	[³H]Norepinephrine content, % of control
7	50	69
10	50	99
9	50	50

Various antihypertensive agents used in clinical therapy cause a release of norepinephrine from the heart,[12] e.g., guanethidine. Therefore, some selected compounds of the present study were tested for their ability to release norepinephrine from the hearts of treated mice. The results of this assay are shown in Table IV. It was found that compound **9** caused a 50% decrease in norepinephrine content at a dose of 50 mg/kg orally. This is comparable with 53% decline in norepinephrine caused by guanethidine at a dose of 50 mg/kg in the same experiments. When the experimental conditions were modified so that compound **9** was given 15 min after, instead of before, labeled norepinephrine, a 44% decline in norepinephrine content was observed at 50 mg/kg while there was a 53% decline at 12.5 mg/kg by guanethidine. These combined results indicate that agents of this series cause an increased release of norepinephrine in the heart. Thus, it is likely that the antihypertensive effect of compound **9** may, at least in part, be mediated through a guanethidine-like mechanism.

The thienylethanolamines of the present study exert their biological activity through an interaction with various receptor sites. The antihypertensive activity observed therefore appears to be mediated by more than one mechanism.

Experimental Section

The infrared and ultraviolet spectra were recorded on a Perkin-Elmer diffraction grating and Unicam spectrometer, respectively. The melting points were taken on a Thomas-Hoover apparatus and are uncorrected. The NMR spectra were performed

on a Varian A-60A spectrometer. Organic extracts were dried over anhydrous magnesium sulfate, and solvents were always removed under vacuum. Merck silica gel 60 (70–230 mesh) was used for column chromatography. The following amines were obtained commercially: *p*-methoxyphenethylamine, 1-(3,4-dimethoxy)- and 1-(3,4,5-trimethoxy)phenylethylamine, 1-(*o*-tolyl)piperazine dihydrochloride, and tryptamine.

3,4-Methylenedioxyphenethylamine Hydrochloride (2). Aluminum chloride (34.6 g) followed by lithium aluminum hydride (9.88 g) was added portionwise to 300 ml of ether cooled in an ice bath. A solution of 3,4-methylenedioxyphenylacetonitrile (50 g) in ether was added at such a rate as to maintain a gentle reflux. The reaction mixture was stirred for an additional 2 h, then cooled in an ice bath, and carefully treated with 15 ml of water followed by 125 ml of 20% sodium hydroxide. The resulting mixture was filtered and the filtrate was treated with anhydrous hydrogen chloride. The title compound obtained as a white solid (70%) was filtered and dried: mp 203–207°; NMR (Me_2SO-d_6) δ 2.9 (m, 4 H, $-CH_2CH_2N$), 6.0 (s, 2 H, OCH_2O), 6.6–6.9 (m, 3 H, aromatic), 8.3 (broad, 3 H, NH_3^+).

α-(2-Thienyl)-4-(*o*-tolyl)-1-piperazineethanol (3). A solution of α-bromomethyl-2-thienylmethanol (10.4 g) in toluene (150 ml) and 1-(*o*-tolyl)piperazine [prepared from 1-(*o*-tolyl)piperazine dihydrochloride (18.7 g) by addition of a stoichiometric amount of sodium hydroxide and extracting the liberated base with chloroform] was refluxed for 24 h, cooled to 25°, and shaken with 10% sodium hydroxide. The organic liquor was extracted with 10% hydrochloric acid; the aqueous layer was washed with chloroform and made alkaline with 20% sodium hydroxide. The base thus liberated was extracted with chloroform and dried, and the solvent was removed to yield a light brown oil, which was purified by chromatography to obtain a homogeneous semisolid (6.5 g, 43%): NMR ($CDCl_3$) δ 2.3 (s, 3 H, $-CH_3$), 2.9 (m, 10 H, $-CH_2-$), 4.0 (broad, 1 H, -OH), 5.1 (t, 1 H, HCO), 7.2 (m, 7 H, aromatics). Treatment of the free base with ethereal HCl gave the hydrochloride **3** in 51% yield: mp 221° dec. Anal. ($C_{17}H_{22}N_2OS$·HCl) C, H, N.

1-(2-Thienyl)-3-[4-(*o*-tolyl)-1-piperazinyl]-1-propanone Dihydrochloride (4). 1-(*o*-Tolyl)piperazine dihydrochloride (6.4 g), 2-acetylthiophene (2.1 g), paraformaldehyde (0.77 g), and 5 drops of concentrated hydrochloric acid were allowed to react together in isoamyl alcohol (50 ml). After refluxing for 4 h the reaction mixture was allowed to stand at room temperature for 48 h. The solid was filtered and the resulting amino ketone was isolated after chromatography on silica gel in 39% yield: ir ($CHCl_3$) 1660 cm^{-1}; NMR ($CDCl_3$) δ 2.25 (s, 3 H, CH_3), 2.5–3.3 (m, 12 H, CH_2), 6.9–7.8 (m, 7 H, phenyl and thienyl H).

Treatment of the free base (2.0 g) with anhydrous hydrogen chloride gave the title compound in 65% yield as a crystalline compound: mp 200°; ir (Nujol) 2350, 1660 cm^{-1}; NMR (Me_2SO-d_6) δ 2.3 (s, 3 H, CH_3), 3.4 (m, 12 H, CH_2), 6.9–8.2 (m, 7 H, phenyl and thienyl H), 10, 11.8 (broad, 2 H, NH_2^+). Anal. ($C_{18}H_{22}N_2OS$·2HCl) C, H, N.

2,5-Dichloro-α-(isopropylaminomethyl)-3-thiophenemethanol Hydrochloride (14). **α-Bromomethyl-2,5-dichloro-3-thienyl Ketone.**[2a] Pyridinium bromide perbromide (PBP, 16.4 g) was added in two portions to a solution of 2,5-dichloro-3-thienylmethyl ketone (commercially available, 10.0 g) in chloroform (60 ml). The reaction mixture was stirred for 1 h, then poured onto ice–water, and extracted with ether. The ethereal extract was washed with water and saturated saline solution, dried, and concentrated. The bromo ketone, purified by chromatography, was obtained as a colorless oil in 79% yield: ir (film) 1685 cm^{-1}; NMR ($CDCl_3$) δ 4.38 (s, 2 H, CH_2Br), 7.25 (s, 1 H, C=CH). **α-Bromomethyl-2,5-dichloro-3-thiophenemethanol.** The bromo ketone (5 g), dissolved in 25 ml of methanol and cooled to 0°, was treated portionwise with sodium borohydride (0.3 g) and stirred for 1 h. The resulting solution was poured into ice–water and extracted with ether. The ethereal extract was washed with water and saturated saline solution, dried ($MgSO_4$), and concentrated. The title compound was obtained in 94% yield as a colorless oil which crystallized on standing: mp 62–63°; ir ($CHCl_3$) 3540 cm^{-1}; NMR ($CDCl_3$) δ 2.75 (d, J = 4 Hz, 1 H, OH), 3.58 (m, 2 H, CH_2Br), 5.05 (m, 1 H, CHO), 6.9 (s, 1 H, C=CH). **2,5-Dichloro-α-(isopropylaminomethyl)-3-thiophenemethanol** was synthesized from bromothiophenemethanol described above, using a pressure bottle as described earlier.[2a] The NMR ($CDCl_3$) exhibited δ 1.05 (d, J = 6 Hz, 6 H, CCH_3), 2.83 (m, 3 H, CHN), 4.78 (m, 1 H, CHO), and 6.90 (s, 1 H, aromatic H). The hydrochloride was prepared in the usual manner and crystallized from ethyl acetate–methanol (63% yield): NMR (Me_2SO-d_6) δ 1.3 (d, J = 6.5 Hz, 6 H, CCH_3), 2.9–3.7 (m, 3 H, CHN), 5.1 (m, 1 H, CHO), 6.4 (m, 1 H, OH), 7.25 (s, 1 H, C=CH), 9.2 (broad, 2 H, NH_2^+). Anal. ($C_9H_{14}Cl_3NOS$) C, H, N.

β-(Isopropylamino)-β-(5-methyl-2-thienyl)ethanol Hydrochloride (20). To a solution of 2-methylthiophene (30.4 g) and acetyl chloride (24.3 g) in dry benzene (100 ml) cooled to 0° was added a solution of stannic chloride (81 g) in benzene (25 ml). The mixture was allowed to reach room temperature and stirred for 72 h. The reaction mixture was poured on ice and extracted with ether. The ether layer was washed and dried and the solvent was removed to yield the crude product. This was chromatographed to yield pure **5-methyl-2-thienyl methyl ketone** (24.9 g, 57%) homogeneous by TLC: ir 1655 cm^{-1}; NMR ($CDCl_3$) δ 2.5 (s, 3 H, CH_3C=C), 2.55 (s, 3 H, CH_3C=O), 6.83 (m, 1 H, HC=C), 7.57 (d, 1 H, HC=C). The above methyl ketone (24.8 g) in chloroform (170 ml) was treated in two portions with PBP (56.7 g) and the mixture stirred for 2.5 h. The resulting solution was poured on ice water and extracted with ether. The ether layer was dried and the solvent removed to yield a brown oil (36.6 g) which was purified through a column to yield a homogeneous **α-bromomethyl-5-methyl-2-thienyl ketone** (24.7 g, 63%): ir 1650 cm^{-1}; NMR ($CDCl_3$) δ 2.56 (s, 3 H, CH_3C=C), 4.3 (s, 2 H, CH_2Br), 6.86 (m, 1 H, HC=C), 7.67 (m, 1 H, HC=C). The reduction of the above ketone (24.5 g) in methanol (110 ml) was conducted at ice-bath temperature and treated with sodium borohydride (1.48 g). The reaction was stirred for 0.5 h, poured in ice–water, and extracted with ether. The ether extract was washed and dried and the solvent was removed to yield **α-bromomethyl-5-methyl-2-thiophenemethanol** as a light yellow oil (21.7 g, 87%): NMR δ 2.47 (m, 4 H, CH_3, OH), 3.6 (m, 2 H, CH_2Br), 5.0 (m, 1 H, CHO), 6.8 (m, 2 H, HC=C).

The reaction of the above bromohydrin (5 g) with isopropylamine was carried out in a pressure bottle at 90° as described before[2a] to yield **β-isopropylamino-β-(5-methyl-2-thienyl)ethanol** (2.43 g, 54%) as a homogeneous oil: NMR δ 1.1 (d, J = 6 Hz, 6 H, CCH_3), 2.45 (s, 3 H, $C{=}CCH_3$), 2.7 (s, 2 H, OH, NH), 2.9 (t, 1 H, CHN–), 3.7 (m, 2 H, CH_2O), 4.0 (m, 1 H, CHN), 6.7 (m, 2 H, HC=C). The hydrochloride **20** of the base (2.32 g) was prepared in the usual manner to give a brown solid (2.4 g, 88%), mp 166–167°. Anal. ($C_{10}H_{18}NOSCl$) C, H, N.

α-(3,4-Dimethoxyphenethylaminomethyl)-5-methyl-2-thienylmethanol Oxalate (10) and β-(3,4-Dimethoxyphenethylamino)-5-methyl-2-thienylethanol Oxalate (21). α-Bromomethyl-5-methyl-2-thienylmethanol (5.0 g) described above and β-(3,4-dimethoxyphenyl)ethylamine (6.2 g) were refluxed in dioxane for 3 h. The mixture was cooled to room temperature, diluted with chloroform (200 ml), washed with 10% sodium hydroxide and water, and dried, and the solvent was evaporated. The residual oil (11.4 g) was chromatographed to yield pure isomer A [2.36 g (34%); NMR ($CDCl_3$) δ 2.45 (s, 3 H, $\gtrless CCH_3$), 3.0 (m, 6 H, CH_2N, CH_2C=C), 3.85 (s, 6 H, CH_3O), 4.45 (broad, 2 H, OH, NH), 5.1 (t, J = 6 Hz, CH_2O), 6.8 (m, 5 H, aromatics)] and isomer B [2.63 g (35%); NMR ($CDCl_3$) δ 2.27 (s, 2 H, CH_2Ar), 2.47 (s, 3 H, $\gtrless CCH_3$), 2.8 (m, 3 H, CHN), 3.7 (m, 2 H, CH_2O), 3.87 (m, 6 H, CH_3O), 6.75 (m, 5 H, aromatics)].

Isomers A and B were converted to their respective oxalates as follows. A solution of free base in ethyl acetate was mixed with a methanolic solution of oxalic acid until acid to litmus. The solution was allowed to stand at room temperature for 2 h and cooled in an ice bath, and the crystals were filtered. Isomer A yielded (50%) oxalate **21**: mp 108–110°; NMR (Me_2SO-d_6) δ 2.45 (s, 3 H, $C{=}CCH_3$), 2.9 (broad, 4 H, CH_2N, CH_2C=C), 3.75 (s, 6 H, CH_3O), 3.82 (m, 2 H, CH_2O), 4.55 (m, 1 H, CHN), 6.6–7.2 (m, 5 H, aromatics), 8.25 (broad, 4 H, OH, NH_2^+, COOH). Isomer B gave oxalate **10** (50%): mp 160°; NMR (Me_2SO-d_6) δ 2.42 (s, 3 H, $C{=}CCH_3$), 3.1 (m, 6 H, CH_2N, CH_2C=C), 3.78 (s, 6 H, CH_3O), 5.2 (m, 1 H, CHO–), 6.8 (m, 5 H, aromatics), 8.3 (broad, 4 H, OH, NH_2^+, COOH). Anal. ($C_{18}H_{25}NO_3S$·$C_2H_2O_4$) C, H, N.

α-(3,4-Methylenedioxyphenethylaminomethyl)-5-methyl-2-thienylmethanol Hydrochloride (12). A solution of

α-bromomethyl-5-methyl-2-thienylmethanol (5.0 g) in toluene (100 ml) was allowed to react with 3,4-methylenedioxyphenethylamine obtained from the corresponding hydrochloride **2** (6.5 g) at reflux temperature for 8 h. The basic products were isolated and purified by chromatography to yield α-(3,4-methylenedioxyphenethylaminomethyl)-5-methyl-2-thienylmethanol (1.74 g, 25%): mp 93–94°; NMR ($CDCl_3$) δ 2.42 (s, 3 H, $CH_3C\leqslant$), 2.8 (m, 6 H, CH_2N, $CH_2C{=}C$), 3.1 (s, 2 H, NH, OH), 4.9 (t, J = 6 Hz, 1 H, CHO–), 5.9 (s, 2 H, OCH_2O), 6.7 (m, 5 H, aromatics). The hydrochloride **12** was prepared in the usual manner and crystallized from methyl ethyl ketone–methanol–ether: mp 183–185°; NMR δ 2.49 (s, 3 H, $CH_3C\leqslant$), 3.1 (m, 6 H, CH_2N, $CH_2C{=}C$), 5.25 (m, 1 H, CHO–), 6.0 (m, 2 H, CH_2O), 6.6–7.2 (m, 5 H, aromatics). Anal. ($C_{16}H_{20}NO_3SCl$) C, H, N.

α-[(3,4-Dimethoxyphenethyl)methyl]aminomethyl-5-methyl-2-thiophenemethanol Oxalate (17). Isomer B (2.29 g) described in the previous experiment was methylated with methyl iodide (9.94 g) in benzene (70 ml) at room temperature over 72 h. The *N*-methyl base (2.35 g) was isolated and purified by chromatography to yield the pure product (1.25 g, 82%): NMR ($CDCl_3$) δ 2.41 (s, 3 H, CH_3N), 2.46 (s, 3 H, $CH_3C{=}C$), 2.6–2.8 (m, 6 H, CH_2N, $CH_2C{=}C$), 3.68 (s, 1 H, OH), 3.83 (s, 3 H, CH_3O), 3.88 (s, 3 H, CH_3O), 4.88 (t, 1 H, CHO–), 6.6–6.9 (m, 5 H, aromatics). The oxalate salt **17** was prepared in the usual manner as described above (51%): mp 149–150°; NMR (Me_2SO-d_6) δ 2.45 (s, 3 H, $>C_3CH_3$), 2.9 (s, 3 H, CH_3N), 3.8 (s, 6 H, CH_3O), 5.3 (m, 1 H, CHO–), 6.85 (m, 5 H, aromatics), 9.0 (s, 3 H, OH, NH, COOH). Anal. ($C_{18}H_{25}NO_3S{\cdot}C_2H_2O_4$) C, H, N.

***N*-(3-Ethylindolyl)-α-(4,5-dichloro-2-thienyl)ethanolamine Hydrochloride (19).** α-Bromomethyl-4,5-dichloro-2-thiophenemethanol (8.7 g) described earlier[2a] was treated with tryptamine (6.44 g) at 75° for 1 h. The resulting mixture was worked up to isolate the free base in the usual manner: mp 43–45°; ir ($CHCl_3$) 3580, 3460 cm^{-1}; NMR ($CDCl_3$) δ 2.8 (m, 2 H, CH_2N), 2.94 (s, 4 H, CH_2N, $CH_2C{=}C$), 3.63 (broad, 2 H, NH, OH), 4.74 (m, 1 H, CHO–), 6.6 (s, 1 H, HC=C), 6.8–7.8 (m, 5 H, aromatics), 8.15 (broad, 1 H, NH). The hydrochloride crystallized from methanol–ethyl acetate: mp 204–205°; ir (Nujol) 3480, 3400, 1606, 1585, 1525 cm^{-1}; NMR (Me_2SO-d_6) δ 3.13 (broad, 6 H, CH_2N, $CH_2C{=}C$), 5.15 (m, 1 H, CHO–), 6.8–7.8 (m, 9 H, NH_2^+, OH, aromatics), 10.8 (s, 1 H, NH). Anal. ($C_{16}H_{17}Cl_3N_2OS$) C, H, N.

***N*-β-(3,4-Dimethoxyphenyl)ethyl-α-(4,5-dichloro-2-thienyl)ethanolamine Hydrochloride (7).** The condensation of α-bromomethyl-4,5-dichloro-2-thiophenemethanol[2a] (7.3 g) and β-(3,4-dimethoxy)ethylamine (13.2 g) at 125° under nitrogen yielded, after the usual workup and chromatography, the free base of **7** (51%): ir ($CHCl_3$) 3600, 1595, 1515, 1465 cm^{-1}; NMR ($CDCl_3$) δ 2.82 (m, 6 H, CH_2N, $CH_2C{=}C$), 3.16 (s, 2 H, OH, NH), 3.90 (s, 6 H, CH_3O), 4.83 (m, 1 H, CHO), 6.76 (m, 4 H, aromatics). Anal. ($C_{16}H_{19}Cl_2NO_3S$) C, H, N. The hydrochloride **7**, prepared as usual (63%), had mp 160–161°: ir (Nujol) 3490, 3340, 1590, 1575, 1550, 1225, 1132 cm^{-1}; NMR (MeOH-*d*) δ 3.25 (m, 6 H, CH_2N, $CH_2C{=}C$), 3.84 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 5.28 (q, 1 H, CHO–), 6.97 (m, 4 H, aromatics). Anal. ($C_{16}H_{20}Cl_3NO_3S$) C, H, N.

4,5-Dichloro-α-[[(*p*-methoxyphenethyl)amino]methyl]-2-thiophenemethanol Hydrochloride (8). The free base of **8** was prepared by refluxing the α-bromomethyl-4,5-dichloro-2-thiophenemethanol[2a] (5.75 g) and the *p*-methoxyphenethylamine in dioxane for 2 h. After purification by chromatography, the base was obtained as a light yellow solid (3.46 g, 50%): NMR ($CDCl_3$) δ 2.8 (m, 6 H, CH_2N, $CH_2C{=}C$), 3.0 (s, 2 H, OH, NH), 4.75 (m, 1 H, CHO), 6.65–7.15 (m, 5 H, aromatics). The base was treated with anhydrous hydrochloric acid gas in methanol–chloroform to yield (63%) hydrochloride salt **8** after crystallization from ethyl acetate: mp 202–203°; NMR (Me_2SO-d_6) 2.7–2.4 (m, 6 H, CH_2N, $CH_2C{=}C$), 3.7 (s, 3 H, OCH_3), 5.3 (m, 1 H, CHO–), 6.75–7.25 (m, 5 H, aromatics), 9.35 (broad, 2 H, NH_2^+). Anal. ($C_{15}H_{18}Cl_3NO_2S$) C, H, N.

4,5-Dichloro-α-(3,4-methylenedioxyphenethylaminomethyl)-2-thiophenemethanol Hydrochloride (9). The free base of **9** was prepared as described above using dioxane (49%): NMR ($CDCl_3$) δ 2.6–2.9 (m, 6 H, CH_2N, $CH_2C{=}C$), 2.95 (s, 2 H, OH, NH), 4.75 (m, 1 H, CHO), 5.92 (s, 2 H, CH_2O), 6.5–6.8 (m, 4 H, aromatics). The hydrochloride **9** had mp 215° dec. Anal. ($C_{15}H_{16}Cl_3NO_3S$) C, H, N.

4,5-Dichloro-α-[(3,4,5-trimethoxyphenylethylamino)methyl]-2-thiophenemethanol Hydrochloride (28). Trimethoxyphenethylamine hydrochloride was prepared using a method described by Kiefer[13]: NMR (Me_2SO-d_6) δ 2.93 (m, 4 H, CH_2N, $CH_2C{=}C$), 3.66 and 3.77 (s, 9 H, OCH_3), 6.55 (m, 2 H, aromatics), 6.68 (s, 3 H, NH_3^+). Anal. ($C_{11}H_{18}ClNO_3$, 247.72) C, H, N. Condensation of α-bromomethyl-4,5-dichloro-2-thiophenemethanol[2a] with the base of the above hydrochloride in dioxane yielded α-3,4,5-trimethoxyphenethylaminomethyl-4,5-dichloro-2-thiophenemethanol as a light brown oil (43%): NMR ($CDCl_3$) δ 2.75 (m, 6 H, CH_2N, $CH_2C{=}C$), 2.9 (s, 2 H, OH, NH), 3.8 (s, 9 H, CH_3O–), 4.75 (m, 1 H, CHO–), 6.33 (s, 2 H, aromatics), 6.66 (s, 1 H, HC=C). The hydrochloride of the above base was prepared in 72% yield: mp 167–168°; NMR (Me_2SO-d_6) δ 3.20 (m, 6 H, CH_2N, $CH_2C{=}C$), 3.66 (s, 3 H, $-OCH_3$), 3.74 (s, 6 H, OCH_3), 5.25 (m, 1 H, CHO–), 6.54 (s, 2 H, aromatics), 7.0 (broad, 3 H, NH_2^+, OH), 7.02 (s, 1 H, HC=C). Anal. ($C_{17}H_{13}Cl_3NO_4S$) C, H, N.

α-[[(3,4-Dimethoxyphenethyl)amino]methyl]-5-phenyl-2-thiophenemethanol Hydrochloride (11). 2-Phenylthiophene[14] (16.0 g) in anhydrous tetrahydrofuran (100 ml) was treated with an equimolar amount of butyllithium at -20°. The resulting solution was poured onto dry ice (ca. 50 g) in ether. When all the dry ice was gone, the reaction mixture was hydrolyzed with water and acidified with dilute hydrochloric acid. The resulting mixture was purified once via the sodium salt, followed by crystallization from carbon tetrachloride, to yield 5-phenyl-2-thiophenecarboxylic acid (16.7 g, 82%): ir ($CHCl_3$) 1665 cm^{-1}; NMR (acetone-*d*) δ 6.4 (broad, 1 H, –OH), 7.3–7.9 (m, 7 H, aromatics).

The above acid (16.7 g) in anhydrous ether (300 ml) was cooled to -50° and treated with 2 equiv of methyllithium. The reaction mixture was brought to 0° and poured onto cold 5% hydrochloric acid and extracted with ether. The ethereal extract was washed with water and dried and the solvent was removed to yield a yellow solid (13.5 g). It was purified by chromatography to yield pure **2-acetyl-5-phenylthiophene** (11.9 g, 86%): mp 115°; ir ($CHCl_3$) 1650 cm^{-1}; NMR ($CDCl_3$) δ 2.55 (s, 3 H, $CH_3C{=}O$), 7.2–7.8 (m, 7 H, aromatics).

The above ketone (11.7 g) was brominated with 1 equiv of bromine in acetic acid. The product was isolated by diluting with water and extracting with chloroform. The crude product was chromatographed to yield α-bromomethyl-5-phenyl-2-thienyl ketone (11.5 g, 71%): mp 114°; NMR ($CDCl_3$) δ 4.2 (s, 2 H, CH_2Br), 7.5 (m, 7 H, aromatics). The bromo ketone (11.5 g) was reduced in methanol (100 ml) and sodium borohydride (0.76 g) to yield the corresponding bromohydrin (8.72 g, 88%), homogeneous by TLC: ir ($CHCl_3$) 3550 cm^{-1}; NMR ($CDCl_3$) δ 2.75 (broad, 1 H, OH), 3.65 (m, 2 H, CH_2Br), 5.1 (m, 1 H, CHO–), 6.9–7.65 (m, 7 H, aromatics).

The bromohydrin (8.6 g) was condensed with β-(3,4-dimethoxyphenyl)ethylamine (8.15 g) in refluxing toluene over 24 h. The resulting crude product was chromatographed to yield pure **α-(3,4-dimethoxyphenethylamino)methyl-5-phenyl-2-thiophenemethanol** (6.33 g, 55%) as a light yellow oil: NMR ($CDCl_3$) δ 2.9 (m, 6 H, CH_2N, $CH_2C\leqslant$), 3.16 (s, 2 H, OH, NH), 3.82 (s, 6 H, CH_3O), 5.0 (m, 1 H, CHO–), 6.75–7.7 (m, 10 H, aromatics). The hydrochloride **11** of the above base was prepared in the usual manner: mp 185°; NMR (Me_2SO-d_6) δ 3.1 (m, 6 H, CH_2N, $CH_2C\leqslant$), 3.75 (s, 6 H, CH_3O), 5.3 (m, 1 H, CHO–), 7.4 (s, 1 H, OH), 6.6–7.7 (m, 5 H, aromatic), 9.4 (broad, 1 H, NH^+). Anal. ($C_{22}H_{25}ClNO_3S$) C, H, N.

Pharmacological Methods. Antihypertensive Assay. (a) The compounds were tested in SHR using the tail-cuff technique[9b] for blood pressure and heart rate measurements. The compounds were administered orally, at doses approximately equal to 25% of the intraperitoneal LD_{50} in mice. Four to eight animals were used in each experiment with an equal number serving as control.

(b) The test in normotensive animals (four to eight per group) for blood pressure and heart rate measurement was carried out via femoral artery cannulation under lidocaine local anesthetic as described.[10] The compounds were administered orally 2 h prior to the test. The changes in blood pressure due to vertical tilt and due to the iv doses of agonists such as angiotensin, epinephrine, isoproterenol, and tyramine were recorded and compared with responses of 70 untreated control rats. Three compounds, **12**,

24, and 11, were also tested at 5 mg/kg iv to evaluate their effect on the pressor response of phenylephrine (consecutive doses of 2, 4, and 8 μg/kg iv). This was done, using groups of six rats per compound, with an equal number serving as saline treated control.

(c) Pithed rats were used in which pressor responses were elicited by electrical stimulation via the pithing rod at a current of 80 V, at a frequency of 10 Hz, and a duration of pulse of 1 ms maintained for 1 s.[11] The compounds were administered iv after recording three reproducible control responses. The stimulation was continued at regular intervals for 45–60 min after the dose. The alteration in the pressor responses, induced by electrical stimulation, was noted after the injection of the compound.

Inhibition of Catecholamine-Induced Lipolysis. Free fatty acid release from rat epididymal fat pad minces was determined by the semiautomated procedure of Kraml[15] based on Itaya's modification[16] of the Duncombe method.[17] The effect on the catecholamine-induced lipolysis was measured by incubating the fat pad minces at 37° for 30 min in the presence of 1×10^{-5} M norepinephrine. The data are expressed as percent inhibition from the controls.

Labeled Norepinephrine Levels in Heart. The effect of the test compound on [^{3}H]norepinephrine level in the mouse heart was determined as described previously.[18] Male albino mice (six to eight per group) were treated with the test compound (50 mg/kg, orally) or water–Tween 80 vehicle, 15 min later, followed by an intravenous injection of [^{3}H]norepinephrine (5–15 Ci/mmol). The animals were sacrificed 5 h after the administration of the test compound. The hearts were removed, frozen, homogenized in 0.4 N perchloric acid, and centrifuged and radioactivity was determined in the supernatant fluid.

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Tetramethoxydibenzoquinolizinium Salts. Preparation and Antileukemic Activity of Some Positional and Structural Isomers of Coralyne

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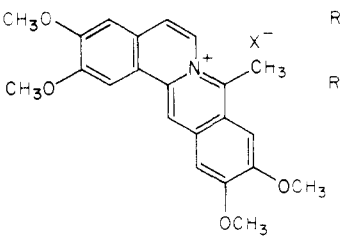
Some positional and structural isomers of coralyne were prepared and evaluated in the P388 lymphocytic leukemia system for their inhibitory activity. The levels of antileukemic activity of coralyne, neocoralyne, isocoralyne, and stracoralyne were comparable, thus implying that two sets of the N–O–O triangular pharmacophore in a condensed isoquinoline molecule are preferable and the angle between these two sets has little influence on antileukemic activity. The importance of the environment around the C_5–C_6 region of the dibenzo[*a*,*g*]quinolizine ring to antileukemic activity was demonstrated by the activity differences between coralyne and allocoralyne.

Preliminary screening results of antileukemic alkaloid coralyne (1) and related alkoxybenzo[*a*,*g*]quinolizinium salts[1,2] accentuated the importance of structural planarity and rigidity of compounds of this type for oncolytic activity. This information, coupled with the structure–activity observations of another series of condensed isoquinoline antileukemic alkaloids including nitidine, fagaronine, and other benzo[*c*]phenanthridines (**2**),[3-10] suggested that two sets, rather than one set, of the N–O–O triangulation feature[11] in one molecule may be more desirable for achieving antileukemic activity.

It therefore appears that a study of the effect of (a) the relative position of the methoxy groups with respect to the isoquinoline N atom, (b) the relative position of the α-methyl group with respect to the quaternized N atom, and (c) the angle between the two-triangulation sets in a



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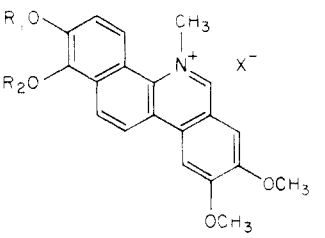

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condensed isoquinoline molecule on the antileukemic activity would be of value. Consequently, three position isomers (**3**, **4**, and **5**) and one structural isomer (**6**) of coralyne were prepared for this study.

Chemistry. 8-Methyl-3,4,10,11-tetramethoxydibenzo[*a*,*g*]quinolizinium acetosulfate (neocoralyne ace-