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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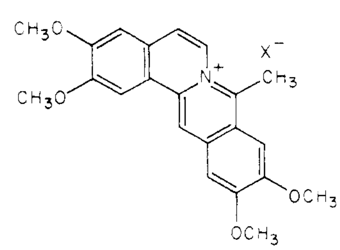
Some positional and structural isomers of coralyne were prepared and evaluated in the P388 lymphocytic leukemia system for their inhibitory activity. The levels of antileukemic activity of coralyne, neocoralyne, isocoralyne, and stracoralyne were comparable, thus implying that two sets of the N–O–O triangular 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.



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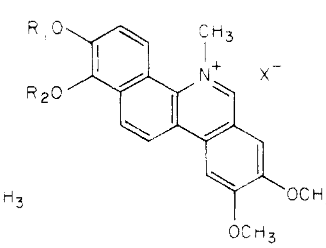

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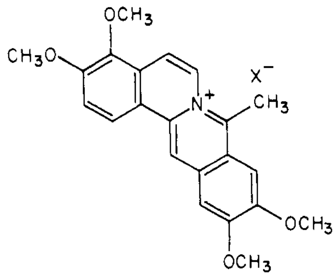
It therefore appears that a study of the effect of (a) the relative position of the methoxy groups with respect to the isoquinoline N atom, (b) the relative position of the α-methyl group with respect to the quaternized N atom, and (c) the angle between the two-triangulation sets in a condensed isoquinoline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



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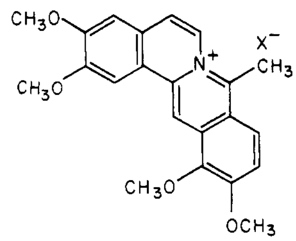

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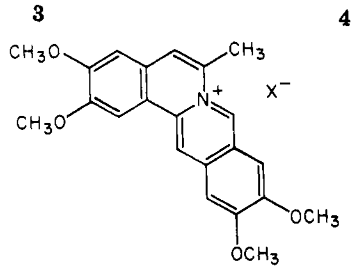

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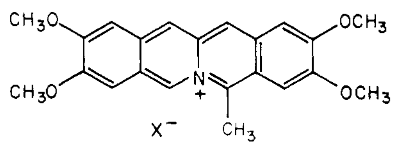

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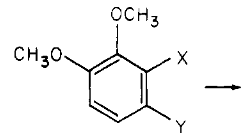
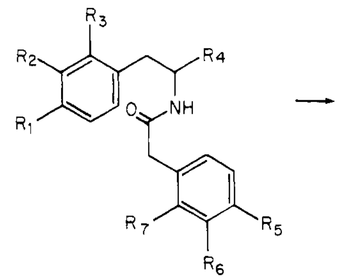
tosulfate, 3, X = $C_2H_3O_5S$), 8-methyl-2,3,11,12-tetramethoxydibenzo[*a*,*g*]quinolizinium acetosulfate (isocoralyne acetosulfate, 4, X = $C_2H_3O_5S$), and 6-methyl-2,3,10,11-tetramethoxydibenzo[*a*,*g*]quinolizinium chloride (allocoralyne chloride, 5, X = Cl) were synthesized in a manner similar to that used for the preparation of coralyne[1] except, in the case of allocoralyne chloride (5, X = Cl), the last cyclization step was carried out in a mixture of $POCl_3$ and DMF instead of in a mixture of Ac_2O and H_2SO_4. 2,3-Dimethoxyphenethylamine (**7b**), a starting material for the synthesis of 3 (X = $C_2H_3O_5S$), was obtained by AlH_3 reduction[12,13] of 1-(2,3-dimethoxyphenyl)-2-nitroethene[14] (**7a**). When the HCl salt of 5,6-dimethoxy-1-(3,4-dimethoxybenzyl)isoquinoline (**10a**) was treated with a hot mixture of Ac_2O and H_2SO_4 according to reaction conditions analogous to those used for the preparation of coralyne and related compounds,[1,2] however, the expected cyclized compound 3 (X = $C_2H_3O_5S$) was not formed. The reaction product was found to be an acetylated derivative which resisted cyclization in either boiling EtOH or acid media, as in the case of 6′-acetoxypapaverine.[2] The desired neocoralyne 3 (X = $C_2H_3O_5S$) was finally obtained by treatment of the free base **10a** with the Ac_2O–H_2SO_4 complex at low temperature followed by heating the resulting dark mixture on a water bath. The overall yield of 3 (X = $C_2H_3O_5S$) from **7a** was 23%.

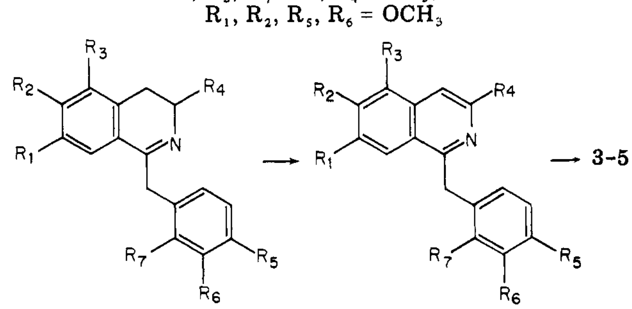
For the synthesis of 4 (X = $C_2H_3O_5S$), one of the starting materials, 2,3-dimethoxyphenylacetic acid[15,16] (**7f**), was prepared by the conventional route via the corresponding alcohol **7c**, the chloride **7d**, and the nitrile **7e**. Compound **7f** was also prepared, albeit in low yield, through the corresponding methyl (methylthio)methyl sulfoxide (**7g**) intermediate by the method of Ogura and Tsuchihashi.[17] The yield of isocoralyne (4, X = $C_2H_3O_5S$) from **10b** was 37% (overall yield from the alcohol **7c**, 14%). The comparatively low yield of 4 (X = $C_2H_3O_5S$) from **10b** could be attributed to an undesired acetylation which took place at position 5 of the benzyl moiety of **10b** during the final cyclization process, thus precluding the formation of 4 (X = $C_2H_3O_5S$).



7a, X = CH=$CHNO_2$; Y = H
b, X = $CH_2CH_2NH_2$; Y = H
c, X = CH_2OH; Y = H
d, X = CH_2Cl; Y = H
e, X = CH_2CN; Y = H
f, X = CH_2CO_2H; Y = H
g, X = CH=C(SCH_3)$SOCH_3$; Y = H
h, X = H; Y = CH=C(CH_3)NO_2
i, X = H; Y = $CH_2CH(CH_3)NH_2$



8a, R_1, R_4, R_7 = H; R_2, R_3, R_5, R_6 = OCH_3
b, R_3, R_4, R_5 = H; R_1, R_2, R_6, R_7 = OCH_3
c, R_3, R_7 = H; R_4 = CH_3; R_1, R_2, R_5, R_6 = OCH_3

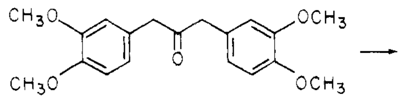


9a, R_1, R_4, R_7 = H; R_2, R_3, R_5, R_6 = OCH_3
b, R_3, R_4, R_5 = H; R_1, R_2, R_6, R_7 = OCH_3
c, R_3, R_7 = H; R_4 = CH_3; R_1, R_2, R_5, R_7 = OCH_3

10a, R_1, R_4, R_7 = H; R_2, R_3, R_5, R_6 = OCH_3
b, R_3, R_4, R_5 = H; R_1, R_2, R_6, R_7 = OCH_3
c, R_3, R_7 = H; R_4 = CH_3; R_1, R_2, R_5, R_6 = OCH_3

The other positional isomer, allocoralyne chloride (5, X = Cl) wherein the position of the methyl group of coralyne was changed, was prepared as follows. Condensation of 3,4-dimethoxybenzaldehyde and nitroethane yielded the substituted nitroethene **7h**. AlH_3 reduction of **7h** gave 1-(3,4-dimethoxyphenyl)-2-propylamine (**7i**). This, in turn, was condensed with 3,4-dimethoxyphenylacetyl chloride and the resulting intermediate **8c** was cyclized and aromatized by standard procedures. Treatment of the free base **10c** with the $POCl_3$–DMF complex under the Vilsmeier–Haack conditions gave allocoralyne chloride. The overall yield was 24% based on the amount of **7i** used.

5-Methyl-2,3,9,10-tetramethoxydibenzo[*b*,*g*]quinolizinium acetosulfate (stracoralyne 6, X = $C_2H_3O_5S$), the linear structural isomer of coralyne, was obtained through the general synthetic route of Wiegrebe et al.[18] using dihomoveratryl ketone (**11**) as the starting material. Compound **11** was obtained by pyrolysis of the lead salt of homoveratric acid. Treatment of the ketone **11** with a mixture of HCO_2H and $HCONH_2$ gave the substituted formamide **12**. Bischler–Napieralski cyclization of **12** with $POCl_3$ in $C_6H_5CH_3$ yielded 6,7-dimethoxy-3-homoveratryl-3,4-dihydroisoquinoline[19,20] (**13**) as a gummy material, which was isolated as a perchlorate salt. Aromatization of the free base **13** by Pd/C under N_2 gave **14**. The latter afforded the desired product **6** (X = $C_2H_3O_5S$) by heating briefly in Ac_2O–H_2SO_4. This product had very low solubility in H_2O and MeOH. In dilute MeOH a yellow fluorescence was noted. Its uv absorption in MeOH was similar to that of coralyne, with an additional intense peak at 347 nm. Analogous to the characteristics of coralyne,[21,22] the aqueous solution of **6** (X = Cl) was also unstable and its maximum uv absorption peak gradually shifted from 298 to 268 nm on overnight standing.



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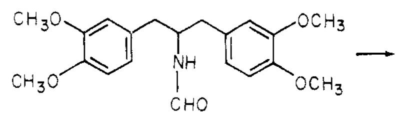

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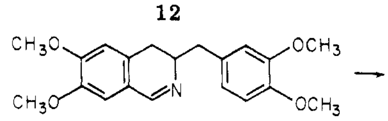

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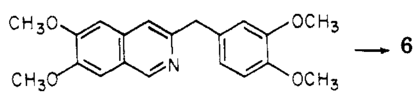

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Although compound **6** prepared by the aforementioned process gave correct elemental analysis, its mass spectrum revealed the presence of a trace amount of dimeric material [m/e 726 and 728 in addition to the expected molecular ion at 364 ($M^+ - C_2H_3O_5S$)]. Conceivably the more linear structure favors some dimerization reaction during the process of cyclization. Attempts to remove this trace amount of the dimeric material by conventional means were not successful.

Biological Activity and Discussion. Antileukemic screening data of coralyne and its positional and structural isomers against leukemia P388 are given in Table I.[23] For a direct comparison of activity, only the results of single dosage given on once daily interval are listed.

Among the positional isomers of coralyne, the antileukemic activity of neocoralyne acetosulfate (**3**, X = $C_2H_3O_5S$) and isocoralyne acetosulfate (**4**, X = $C_2H_3O_5S$) is comparable with that of coralyne acetosulfate (**1**, X = $C_2H_3O_5S$), suggesting that the angle between the two triangulation sets has little influence on antileukemic activity. A smaller angle, on the other hand, does seem to increase toxicity to the host, as indicated by the survival rate of isocoralyne. On the other hand, changing the position of the α-methyl group of coralyne from 8 to 6 decreases the activity and the survival time to the host, as evidenced by the test results of allocoralyne chloride (**5**, X = Cl[24]). This information, together with the reports that the 5,6-dihydrocoralyne showed no antileukemic activity[2] and that the 8-ethyl homologue of coralyne possessed excellent antileukemic activity but the corresponding 8-propyl homologue was inactive,[2] substantiates the importance of the environment around the C_5–C_6 region of the dibenzo[*a*,*g*]quinolizine ring to antileukemic activity for compounds of this type.

The activity exhibited by the structural isomer, stracoralyne (**6**), is of interest. That the activity of **6** (X = $C_2H_3O_5S$) is comparable to that of coralyne further substantiates the significance of the N–O–O triangulation pharmacophore to antileukemic activity for future design of other types of compounds for oncolytic study.

Table I. Antileukemic Activity of Coralyne and Positional and Structural Isomers against Leukemia P388

Compound	Dose, mg/kg	Survival	Wt difference	T/C
1, X = $C_2H_3O_5S$	160	19/24	−2.3	170
	128	25/26	−5.2	167
	100	24/24	−4.2	176
	80	35/36	−2.1	175
	75	19/20	−2.3	175
	64	118/118	−3.1	182
	50	42/42	−2.9	180
	40	28/30	−1.2	173
	32	77/78	−2.4	175
	20	29/30	−1.0	173
	10	28/30	−0.5	159
	8	76/78	−1.5	150
	5	30/30	−0.5	157
2, X = $C_2H_3O_5S$	120	12/12	−2.0	179
	100	6/6	−5.0	209
	80	12/12	−1.9	170
	50	6/6	−3.9	174
	40	11/12	−1.5	153
	25	6/6	−2.8	164
	20	12/12	−1.4	154
	10	6/6	−2.6	149
4, X = $C_2H_3O_5S$	168	0/6		
	60	4/6	−2.1	
	40	11/12	−3.5	177
	20	12/12	−2.3	171
	10	12/12	−1.4	136
	5	12/12	−1.8	127
5, X = Cl	400	5/6	−2.9	131
	200	6/6	−3.7	139
	100	6/6	−3.0	134
	50	6/6	−3.3	134
	25	6/6	−3.6	139
6, X = $C_2H_3O_5S$	160	6/6	−4.2	200
	120	6/6	−3.3	150
	80	6/6	−2.5	180
	40	6/6	−1.7	150
	20	6/6	−0.6	180
	10	6/6	−0.9	145
	5	6/6	−0.8	140

Experimental Section

Melting points were taken with a Thomas-Hoover melting point apparatus. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values.

2,3-Dimethoxyphenethylamine (7b). To a stirred suspension of 40 g (1.05 mol) of $LiAlH_4$ in 800 ml of dry THF cooled at 0° was added dropwise 26 ml of concentrated H_2SO_4 in 50 min. The mixture was stirred at 0° for 30 min. To this was added dropwise 46 g (0.22 mol) of 1-(2,3-dimethoxyphenyl)-2-nitroethene[14] (**7a**) in 1000 ml of dry THF in 2.5 h. The resulting mixture was stirred at 0° for 1 h and then at room temperature for 22 h. It was decomposed by successive addition of H_2O (40 ml), 5% NaOH (170 ml), and 10% NaOH (100 ml). After stirring for 30 min, the mixture was filtered. The solid was stirred with 1500 ml of Et_2O and filtered again. The combined filtrate was dried (K_2CO_3), evaporated to a syrup, and distilled in vacuo to give 41 g of **7b**: bp 108–110° (0.8 min). The product, which gave a single spot in TLC, was used directly for the preparation of *N*-(2,3-dimethoxyphenethyl)-2-(3,4-dimethoxyphenyl)acetamide (**8a**) without further purification.

5,6-Dimethoxy-1-(3,4-dimethoxybenzyl)isoquinoline (10a). To a stirred suspension of 4.5 g of 10% Pd/C in 90 ml of tetralin was added a solution of 25 g (0.073 mol) of 1-(3,4-dimethoxybenzyl)-5,6-dimethoxy-3,4-dihydroisoquinoline (**9a**, prepared from **8a** by the method of Lindenmann[14]) in 150 ml of benzene. The mixture was heated under N_2 while benzene was slowly distilled. The residual suspension was heated at 240–245° under N_2 for 2.5 h with stirring. The reaction mixture was cooled, stirred with 750 ml of $CHCl_3$ for 20 min, and filtered. The solid cake was extracted with $CHCl_3$ (2 × 200 ml). The combined $CHCl_3$ solution was evaporated in vacuo to a syrup to which was added 80 ml of saturated ethanolic HCl and 30 ml of $CHCl_3$. The mixture was added dropwise, with stirring, into 2500 ml of Et_2O. The resulting solid was collected by filtration, washed with Et_2O (2 × 150 ml) and petroleum ether (2 × 200 ml), and dried to give 17 g (65% overall yield from **8a**) of the HCl salt of **10a**: mp 206–208°. Anal. ($C_{20}H_{21}NO_4 \cdot HCl \cdot 0.5H_2O$) C, H, N.

8-Methyl-3,4,10,11-tetramethoxydibenzo[*a,g*]quinolizinium Acetosulfate (Neocoralyne Acetosulfate, 3). A solution of 4.1 g (1.1 mmol) of the HCl salt of **10a** in 300 ml of $CHCl_3$ was neutralized with dilute aqueous Na_2CO_3; the $CHCl_3$ layer was separated, washed with H_2O, dried (Na_2SO_4), and evaporated to yield 3.5 g of the free base **10a**. To this was added a mixture of Ac_2O–H_2SO_4 (prepared by heating a mixture of 14 ml of Ac_2O and 2.8 ml of concentrated H_2SO_4 at 85–95° for 15 min and cooling to room temperature) with ice-bath cooling. The resulting mixture was gradually heated to 90°, then kept at that temperature for 30 min, and cooled. To the reaction solution was added 120 ml of absolute EtOH with stirring and cooling. After overnight standing, the resulting solid product was collected by filtration, washed successively with EtOH (2 × 20 ml), Et_2O (3 × 50 ml), and petroleum ether (3 × 50 ml), and dried to give 2.9 g (52% yield) of **3** as a yellow powder: mp 260–262° dec. An analytical sample was prepared by recrystallization from MeOH: mp 267–269° dec; λ^{EtOH}_{max} 235 nm (log ϵ 4.24), 317 (4.76), 352 (4.19), 376 (4.00), 400 (3.95), and 420 (3.89). Anal. ($C_{24}H_{25}NO_9S \cdot H_2O$) C, H, N.

2,3-Dimethoxyphenylacetic Acid (7f). Method A. To a mixture of 125 g (0.74 mol) of 2,3-dimethoxybenzyl alcohol (**7c**) in 300 ml of $CHCl_3$ was added dropwise, with cooling and stirring, 160 g (1.34 mol) of $SOCl_2$ in 2 h. The resulting solution was then heated at 45° for 1 h and allowed to stand overnight. The solvent and excess $SOCl_2$ were removed under reduced pressure to leave 155 g of the crude chloride **7d** as an oil. This was dissolved in 100 ml of Me_2SO and the solution was added dropwise, with cooling, into a stirred suspension of 100 g (2.04 mol) of NaCN in 200 ml of Me_2SO over 30 min. The mixture was stirred in an ice bath for 2 h and then at room temperature for 24 h. After the addition of 500 ml of cold H_2O, the reaction mixture was extracted with Et_2O (4 × 600 ml). The Et_2O layer was washed with H_2O (4 × 500 ml) and dried (Na_2SO_4). The aqueous extracts were reextracted with Et_2O (4 × 600 ml) and back-extracted with H_2O (4 × 500 ml). The combined Et_2O extract (ca. 4 l.) was dried (Na_2SO_4) and the solvent evaporated in vacuo to give 135 g of the nitrile **7e** as an oil. The yield of **7e** from **7c** was practically quantitative.

The nitrile **7e**, 112 g (0.63 mol), was dissolved in 400 ml of EtOH and added to 1600 ml of 10% aqueous NaOH. The mixture was refluxed for 10.5 h with stirring. The reaction solution was concentrated under reduced pressure to ca. 1000 ml, cooled, and extracted with Et_2O (3 × 250 ml). The aqueous layer was acidified with 380 ml of concentrated HCl. The resulting mixture was extracted with benzene (4 × 400 ml), and the benzene extract was washed with H_2O (3 × 250 ml) and dried (Na_2SO_4). The volume of the dried solution was concentrated to 150 ml and poured, while still warm, into 400 ml of petroleum ether (bp 62–69°) with stirring. After overnight standing, the resulting solid product was collected by filtration, washed with petroleum ether (2 × 50 ml), and dried to give 95 g (77% yield) of **7f**, mp 75–79°. An analytical sample was obtained by recrystallization from EtOH–petroleum ether, mp 80–82°. The product was identical with that prepared by peroxide oxidation of 2,3-dimethoxyphenylpyruvic acid (mp 84°[15]) or by methylation of 2-hydroxy-3-methoxyphenylacetic acid (mp 79–80°[16]).

Method B. A mixture of 20 g (0.12 mol) of 2,3-dimethoxybenzaldehyde, 15 g (0.12 mol) of methyl methylsulfinylmethyl sulfide,[17] and 12 ml of 40% *N*-benzyltrimethylammonium hydroxide (Triton B) in 30 ml of THF was refluxed on a steam bath for 6 h. The solvent and excess reagent were removed under reduced pressure and the residue was purified through a SiO_2 column to give 31 g (95% yield) of [1-(2,3-dimethoxyphenyl)-2-methylsulfinyl-2-methylthio]ethene (**7g**) as an oil. Anal. ($C_{12}H_{16}O_3S_2$) C, H, N.

To a stirred solution of 30 g of **7g** in 80 ml of dimethoxyethane was added, with cooling, 15 ml of concentrated HCl. The mixture was allowed to stir at room temperature for 24 h and then decomposed with 500 ml of 10% Na_2CO_3. The aqueous layer was separated and extracted with Et_2O (4 × 100 ml) and the Et_2O extracts were back-extracted with H_2O (2 × 50 ml). The combined aqueous solution was acidified with 80 ml of concentrated HCl and extracted with $CHCl_3$ (2 × 50 ml). The $CHCl_3$ extract was washed with H_2O (2 × 30 ml) and dried (Na_2SO_4). Evaporation of the solvent gave an oil, which solidified upon trituration with 30 ml of petroleum ether (bp 35–60°). The solid was collected by filtration and washed with petroleum ether to give 3.5 g (16% yield) of **7f**: mp 81–83°. It was found to be identical with that prepared by method A.

***N*-(3,4-Dimethoxyphenethyl)-2-(2,3-dimethoxyphenyl)acetamide (8b).** Into a stirred solution of 19.6 g (0.1 mol) of **7f** in 150 ml of dry $CHCl_3$ was added, with cooling, 36 g (0.3 mol) of $SOCl_2$ in 10 min. The mixture was stirred for 30 min at 0°, slowly warmed to room temperature, and then heated at 50° for 3 h. The solvent and excess $SOCl_2$ were removed under reduced pressure and the residue (ca. 25 g) was dissolved in 260 ml of anhydrous Et_2O. This was added dropwise, with cooling during 30 min, to a stirred mixture of 23.5 g (0.13 mol) of 3,4-dimethoxyphenethylamine, 420 ml of 1 N KOH, and 60 ml of Et_2O. After the addition was complete, the mixture was stirred at 0° for 3 h and the solid product, which precipitated during the reaction, was collected by filtration, washed with H_2O (3 × 100 ml), and dried to give 36 g (quantitative yield) of **8b**: mp 127–128°. Recrystallization from benzene and petroleum ether afforded an analytical sample: mp 130–132°. Anal. ($C_{20}H_{25}NO_5$) C, H, N.

6,7-Dimethoxy-1-(2,3-dimethoxybenzyl)isoquinoline (10b). A solution of 24 g (0.066 mol) of **8b** in 200 ml of dry $CHCl_3$ was added to a stirred suspension of 28 g of PCl_5 in 80 ml of $CHCl_3$ in 10 min. The mixture was stirred at 0° for 1 h and then at room temperature for 3 days under N_2. To this was added, with stirring, 500 ml of Et_2O, and the resulting solid was collected by filtration to give 31 g of the crude HCl salt of 1-(2,3-dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (**9b**). This was dissolved in 800 ml of $CHCl_3$ and stirred vigorously with 200 ml of ice water. The $CHCl_3$ layer was separated, washed with 10% NaOH (2 × 250 ml) and H_2O (3 × 100 ml), and dried (Na_2SO_4). Evaporation of solvent gave 20 g (88% yield) of **9b** as a gummy syrup. It was dissolved in 100 ml of C_6H_6 and added to a mixture of 4.3 g of 10% Pd/C in 40 ml of tetralin. Benzene was then removed from the mixture and the latter was heated at 245–250° for 3 h under N_2. It was cooled and diluted with 300 ml of $CHCl_3$. The catalyst was removed by filtration and the filtrate evaporated in vacuo to a syrup. To this was added 100 ml of 30% ethanolic HCl and the resulting mixture added slowly, with stirring, to 1200 ml of Et_2O. After 3 h of standing, the supernatant liquid was decanted and the residue was dissolved in 350 ml of $CHCl_3$. A 20-ml portion of the $CHCl_3$ solution was added to 300 ml of Et_2O. The precipitated solid was collected by filtration and washed with Et_2O and petroleum ether to give 0.8 g of the HCl salt of **10b**: mp 192–194° dec; λ^{EtOH}_{max} 239 nm (ϵ 4.78), 272 (3.77), 312 (3.68), and 326 (3.71). Anal. ($C_{20}H_{21}NO_4 \cdot HCl \cdot H_2O$) C, H, N.

The remaining $CHCl_3$ solution was neutralized with 150 ml of 10% NH_4OH and extracted with $CHCl_3$ (3 × 300 ml). The $CHCl_3$ extract was washed with H_2O (3 × 250 ml) and dried (Na_2SO_4). Evaporation of the solvent gave 11 g (58% yield) of the free base **10b**, to be used for the following cyclization.

8-Methyl-2,3,11,12-tetramethoxydibenzo[*a,g*]quinolizinium Acetosulfate (Isocoralyne Acetosulfate, 4). A mixture of 8 ml of Ac_2O and 1.6 ml of concentrated H_2SO_4 was heated at 80–90° for 15 min until a red wine color appeared. The cooled liquid was added to 2 g of **10b**. The mixture was heated slowly to 85–90° and was kept at this temperature range for 30 min. It was cooled and diluted with 80 ml of EtOH. After stirring at 0° for 30 min, the resulting solid was collected by filtration, washed successively with EtOH (5 ml), Et_2O (2 × 5 ml), and petroleum ether (2 × 5 ml), and dried to give 1.1 g (37% yield) of **4**: mp 253–255° dec. An analytical sample was obtained by recrystallization from a mixture of MeOH and Et_2O: mp 256–257° dec; λ^{MeOH}_{max} 236 nm (log ϵ 4.48), 248 (4.42), 269 (4.36), 277 (4.39), 317 (4.66), 410 (4.15), 430 (4.13), and 451 (4.08). Anal. ($C_{24}H_{25}NO_9S$) C, H, N.

***N*-(3,4-Dimethoxyphenyl-2-propyl)-2-(3,4-dimethoxyphenyl)acetamide (8c).** To a stirred solution of 8.5 g (0.043 mol) of 3,4-dimethoxyphenylacetic acid in 50 ml of $CHCl_3$ was added dropwise, with cooling, 11 g (0.092 mol) of $SOCl_2$. After the addition was complete, the mixture was kept at 50° for 2 h. The solvent and excess $SOCl_2$ were evaporated under reduced pressure to a reddish oily residue. This was dissolved in 100 ml of Et_2O and the resulting solution was dropped during 10 min, with cooling, into a stirred solution of 1-(3,4-dimethoxyphenyl)-2-propylamine (8 g, 0.041 mol) in a mixture of 100 ml of Et_2O and 80 ml of 8% aqueous NaOH. After the addition was complete, the mixture was stirred continuously in an ice bath for 3 h. The resulting white solid was collected by filtration, washed with H_2O (2 × 50 ml), and dried to give 10.9 g (71% yield) of the amide **8c**: mp 125°. Recrystallization from EtOH–petroleum ether (bp 62–69°) yielded an analytical sample: mp 126–128°. Anal. ($C_{21}H_{27}NO_5$) C, H, N.

6,7-Dimethoxy-1-(3,4-dimethoxybenzyl)-3-methylisoquinoline (10c). To a stirred suspension of 10.2 g (0.048 mol) of PCl_5 in 50 ml of $CHCl_3$ was added, with cooling, a solution of 9 g (0.024 mol) of **8c** in 100 ml of $CHCl_3$. The resulting brown solution was stirred under N_2 in an ice bath for 2 h and then at room temperature for 2 days. Anhydrous Et_2O (350 ml) was then added. The mixture was stirred in an ice bath for 1 h and the solid collected by filtration. It was washed with Et_2O (2 × 50 ml) and dried to give 10 g of the HCl salt of the dihydroisoquinoline **9c**. This was dissolved in 300 ml of $CHCl_3$ and washed with 10% NH_4OH (2 × 100 ml) and the $CHCl_3$ solution was dried (Na_2SO_4). The aqueous layer was extracted with 150 ml of $CHCl_3$ and the organic layers were combined. After drying, the solvent was removed under reduced pressure to give 9 g of the 3,4-dihydroisoquinoline **9c** as a free base. This was dissolved in 100 ml of $C_6H_5CH_3$ and added to a mixture of 3 g of 10% Pd/C in 30 ml of tetralin. Toluene was distilled from the resulting mixture under N_2 and the tetralin suspension was heated under N_2 at 230–250° for 3 h. The catalyst was removed by filtration, washed with $CHCl_3$ (3 × 15 ml), and discarded. To the combined filtrate and washings was added, with stirring, 25 ml of 40% ethanolic HCl. The resulting solution was filtered into 800 ml of Et_2O with cooling and stirring. The precipitated off-white solid was collected by filtration, washed with Et_2O (2 × 50 ml) and petroleum ether (bp 35–60°, 2 × 50 ml), and dried to give 7.3 g (78% overall yield) of the HCl salt of **10c**: mp 175° dec. An analytical sample was obtained as white crystals by recrystallization from EtOH–Et_2O: mp 225–227°. Anal. ($C_{21}H_{23}NO_4 \cdot HCl \cdot 0.5H_2O$) C, H, N.

6-Methyl-2,3,10,11-tetramethoxydibenzo[*a,g*]quinolizinium Chloride (Allocoralyne Chloride, 5, X = Cl). The aforementioned compound (7.1 g) was converted to the free base by the usual base–$CHCl_3$ extraction method. The gummy material (**7g**) was dissolved in 50 ml of redistilled DMF and added to the Vilsmeyer reagent (prepared by addition of 16 ml of distilled $POCl_3$ to 24 ml of pure DMF with cooling; the solution was stirred 1 h prior to use). The mixture was heated at 100–105° under N_2 for 5.5 h. It was cooled in an ice bath. To this was added 200 ml of iced water and the mixture stirred for 30 min. It was followed by addition of 30 g of NaCl. The resulting yellow solid product was collected by filtration, washed with 50 ml of brine water and 50 ml of Et_2O, and dried to give 3.6 g (43% yield) of the product as crystals: mp 248–250°. Recrystallization from MeOH raised the mp to 295–297°. The dilute methanolic solution of allocoralyne showed an intense green fluorescence, characteristic of the coralyne-type compounds: m/e 364 (12%, $M^+ - 3H_2O -$ Cl); λ^{EtOH}_{max} 240 nm (log ϵ 4.44), 281 (4.68), 299 (4.81), 310 (4.82), 330 (4.66), 360 (3.98), 410 (4.22), and 425 (4.27); NMR (CF_3CO_2H, Me_4Si) τ 1.75 (1 H, s, H_1), 2.15 (1 H, s, H_4), 2.60 (1 H, s, H_5), 6.95 (3 H, s, CH_3), 0.37 (1 H, s, H_8), 2.33 (1 H, s, H_9), 2.40 (1 H, s, H_{12}), 0.68 (1 H, s, H_{13}), 5.78 (3 H, s, CH_3O), 5.82 (6 H, s, $2CH_3O$), 5.85 (3 H, s, CH_3O). Anal. ($C_{22}H_{22}ClNO_4 \cdot 3H_2O$) C, H, N.

The uv spectrum of allocoralyne resembled that of coralyne. Their NMR proton assignments were also comparable except, as expected, the doublet of H_5 and H_6 in coralyne with coupling constant J_{H_5,H_6} = 8 Hz was replaced in allocoralyne by a singlet of H_5 at τ 2.60, with an additional acidic proton H_8 at τ 0.37.

5-Methyl-2,3,9,10-tetramethoxydibenzo[*b,g*]quinolizinium Acetosulfate (Stracoralyne Acetosulfate, 6, X = $C_2H_3O_5S$). To 60 ml of Ac_2O was added 4 ml of concentrated H_2SO_4 with stirring and cooling. The solution was heated at 90–95° for 10 min. To the resulting red, wine-colored solution was added 5 g of the HCl salt of 6,7-dimethoxy-3-homoveratryl-3,4-dihydroisoquinoline (**14**) and the mixture was heated at 85–90° for 10 min whereupon an orange-colored solid separated. The reaction mixture was cooled and diluted with 40 ml of MeOH. The orange solid was collected by filtration, washed with MeOH (2 × 5 ml) and Et_2O (2 × 15 ml), and dried to give 3.2 g (48% yield) of the cyclized product: mp 318–320°; m/e 364 (16.3%, $M^+ - C_2H_3O_5S$), 365 ($MH^+ - C_2H_3O_5S$), 726 (19%, $2M^+ - 2C_2H_4O_5S$), 728 (3.1%, $2M^+ - 2C_2H_3O_5S$); λ^{MeOH}_{max} 246 nm (log ϵ 4.14), 270 (4.17), 300 (4.46), 311 (4.83), 332 (4.57), 347 (4.56), 403 (3.83), and 426 (4.15). Anal. ($C_{24}H_{25}NO_9S \cdot H_2O$) C, H, N.

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