counted using a Coulter counter. A control untreated set of cultures and Me_2SO-treated cultures were included for each separate dose–response experiment. Duplicate counts were taken on each well and were usually in agreement with each other (±10%).

From the data obtained, a dose–response curve was drawn, and the ID_{50} and its confidence limits were calculated as in our previous studies.[24]

Substituent Constants. The values for the substituent constants in Table I were taken from our recent compilation.[14]

Collinearity of Variables. The following squared correlation matrix shows that there is little collinearity among the variables used to formulate eq 1–8.

	π	MR_3	$\Sigma\sigma$
π	1	0.17	0.00
MR_3		1	0.03
$\Sigma\sigma$			1

Synthesis and Biological Evaluation of Novel Pyrimidine Nucleoside Analogues of 1,4-Oxathiane, 1,4-Dithiane, and 1,4-Dioxane

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Nine pyrimidine nucleoside analogues, in which the group attached at N-1 is a six-membered ring containing two heteroatoms, have been synthesized using the Vorbrüggen and Bennua (Vorbrüggen, H.; Bennua, B. *Tetrahedron Lett.* **1978**, 1339) coupling procedure. These are 1-(1,4-oxathian-3-yl)-5-fluorouracil (**8**), 1-(4-oxo-1,4-oxathian-3-yl)-5-fluorouracil (two stereoisomers **9** and **10**, resolved by silica gel column chromatography), 1-(1,4-oxathien-3-yl)-5-fluorouracil (**11**), 1-(1,4-oxathian-2-yl)-5-fluorouracil (**12**), 1-(1,4-dithian-2-yl)-5-fluorouracil (**15**), 1-(1,4-dithian-2-yl)uracil (**16**), 1-(1,4-dithian-2-yl)thymine (**17**), and 1-(1,4-dioxan-2-yl)-5-fluorouracil (**20**). All of the analogues were tested for cell-growth inhibition using mouse and human tumor cell lines. The ID_{50} values of all of the analogues are greater than 10^{-4} M, except in the case of **11** using the L1210 cell line. The most active analogues found are compounds **11** and **17**, which were found to be 100 and 200 times less active, respectively, than 5-fluorouracil in the human erythroleukemia cell line, K-562.

The fluorinated pyrimidines were first demonstrated as potentially useful chemotherapeutics by Heidelberger et al. in 1957.[2] Since that time, many derivatives of the clinically useful drug 5-fluorouracil (5-FUra) have been synthesized in the hope of discovering compounds having lower toxicity and improved antitumor activity than does 5-FUra.[3] Many of these derivatives have been shown to slowly release 5-FUra in vivo, and thus they function as relatively nontoxic reservoirs of 5-FUra.[3c,4] In addition to the reduced toxicity, some of these derivatives, including N^1-acetyl-N^3-*o*-toluyl-5-fluorouracil,[3c] 1,3-bis(tetrahydro-2-furanyl)-5-fluorouracil, and 1-(tetrahydro-2-furanyl)-5-fluorouracil (Ftorafur),[4a] offer the convenience of oral administration; also, their relatively long half-lives within the animal body allow the achievement of long lasting and much higher blood and tissue concentrations of 5-FUra than is possible with 5-FUra itself, which is administered by continuous intravenous infusion.[5] Improved tumor affinity appears to have been achieved with 1,3-bis(tetrahydro-2-furanyl)-5-fluorouracil which, compared to Ftorafur, gives not only much higher tissue concentration of 5-FUra but also a relatively higher concentration of 5-FUra in tumor tissue than in normal tissue.[4a] More recently, 5′-deoxy-5-fluorouridine, a new orally active antitumor agent, was reported[3b,6] to offer significant advantages in terms of activity and toxicity over 5-FUra, Ftorafur, and 5-FdUrd.

In contrast to the large number of derivatives of 5-FUra, in which the group attached to N-1 contains a five-membered ring,[3-6] there have been relatively few derivatives, synthesized and screened for activity, in which this group contains a six-membered ring.[3j] The observation that various purines substituted at N-9 with 1,4-dithiane, 1,4-dioxane, or 1,4-oxathiane possessed significant antitumor activity[7] prompted the preparation of 5-FUra derivatives containing these heterocyclic rings. A recent communication has described[8] the preparation of compounds **12** and **20** by the lewis-acid-catalyzed condensation of trimethylsilyloxyalkanal dialkyl acetals with 2,4-bis(trimethylsilyl)-5-fluorouracil, although no data were reported on their biological activities. The present article describes the synthesis of various such compounds and their effects on the growth of a variety of tumor cells in tissue culture.

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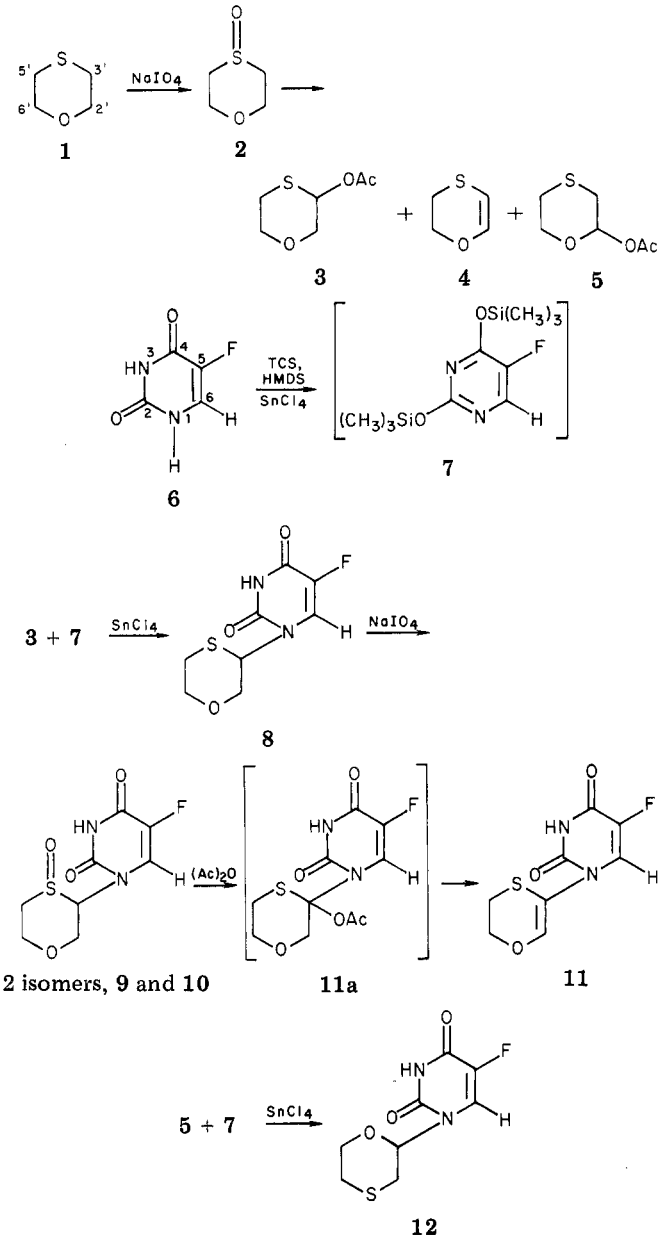
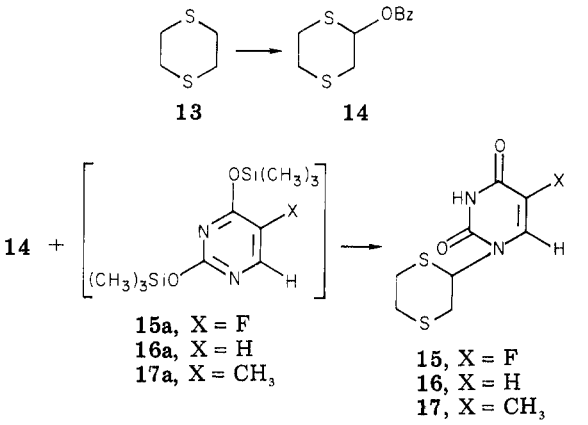
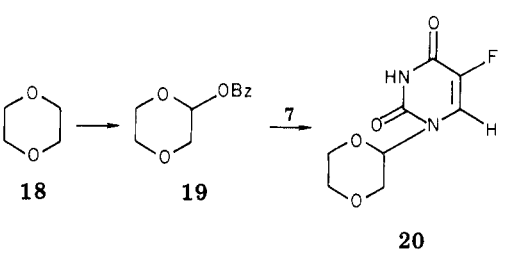
Scheme I



Scheme II



Scheme III



Chemistry. The two regioisomeric nucleoside derivatives of 1,4-oxathiane, namely, compounds **8** and **12**, were prepared by coupling the respective acetoxy derivatives of 1,4-oxathiane (**3** and **5**) with 2,4-bis(trimethylsilyl)-5-fluorouracil (**7**) (see Scheme I) using the procedure of Vorbrüggen and Bennua.[1] This coupling proceeds smoothly at ice-bath temperature, giving a single product in each case. 3-Acetoxy-1,4-oxathiane was prepared as described previously;[9] however, for the preparation of 2-acetoxy-1,4-oxathiane, the Pummerer reaction conditions were modified by increasing the reaction temperature to that of refluxing toluene. Under these conditions the 3-acetoxy derivative **3** is formed first, which then eliminates acetic acid to produce the olefin **4**, followed by the appearance of the 2-acetoxy derivative **5**. The two sulfoxide isomers (**9** and **10**) were produced by oxidation, using sodium metaperiodate, of compound **8** at room temperature. Treatment of either of these sulfoxides with hot acetic anhydride (115 °C) gave the unsaturated analogue **11**, which is presumed to be formed by way of the intermediacy of 1-(3-acetoxy-1,4-oxathian-3-yl)-5-fluorouracil (**11a**).

The dithiane analogues **15–17** (Scheme II) were prepared by coupling 2-(benzoyloxy)-1,4-dithiane (**14**) with their respective 2,4-bis(trimethylsilyl)pyrimidines **15a–17a**. The coupling method for the dithiane analogues was the same as that for the oxathiane analogues, except that it was necessary to raise the coupling temperature to room temperature. 2-(Benzoyloxy)-1,4-dithiane (**14**) was prepared by heating at reflux temperature benzoyl peroxide and an excess of 1,4-dithiane (**13**) in benzene using CuCl as catalyst.[10]

The coupling procedure for the dioxane analogue (**20**), which was prepared from 2-(benzoyloxy)-1,4-dioxane (**19**) and **7** (Scheme III), was identical with that used for the oxathiane analogues. 2-(Benzoyloxy)-1,4-dioxane (**19**) was prepared from 1,4-dioxane (**18**) as described previously.[10]

The ^{1}H NMR spectra of the analogues in acetone-d_6 show some interesting conformational preferences.[11,12] The vicinal coupling constants for the protons at positions 2′ and 3′ indicate that the two oxathiane regioisomers (compound **8** and **12**) show the same conformational preferences as was observed for the corresponding purine derivatives.[9,12] The regioisomer **12** has the 5-fluorouracil group predominantly in the equatorial orientation. The coupling constants observed for the OCH_2CH_2S fragment are virtually identical with those observed in the case of *trans*-2,3-dichloro-1,4-oxathiane (see ref 11b), which is a conformationally fixed compound having the chlorines diaxial. In the case of the regioisomer **8**, the vicinal coupling constants of the H-3′ proton indicate that the 5-fluorouracil group exists preferentially in the axial orientation. The coupling constants observed for the OCH_2C-

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Table I. Effect of Various Nucleoside Analogues on Tumor Cell Growth [a]

compd	ID_{50}, [b] mmol/L K-562 [c]	L1210 [d]	MDAY-D2 [e]
Ftorafur [f]		0.0084	
5-FUra	0.0046;	0.0010; 0.00023;	0.00020
(6)	0.0023	0.00018	
8	>1.05; >1.06	>1.06	4.6
9	>0.99		
10	>1.01		
11	0.38	0.020	
12	>1.00; 0.46	>1.01	1.4
15	>1.02	0.65; 0.23	0.50
16	>1.05	0.24	
17	0.67	0.23; 0.21	
20	>1.09; >0.97	>0.97	>1.00

[a] Reference 18. [b] Dose which inhibits cell-number increase to 50% of the control. [c] Human erythroleukemia. [d] Mouse myeloid leukemia. [e] Reference 19. [f] Ftorafur (99%) was purchased from Aldrich Chemical Co., Inc.

H_2S fragment, although quite different from those for compound **12**, are virtually identical with those found for 2,3,3-trichloro-1,4-oxathiane (see ref 11b), a conformationally fixed compound which probably has a substantially deformed chair conformation.[11b,13]

In the three dithiane derivatives (**15–17**) and in the dioxane derivative (**20**) the pyrimidine group exists preferentially in the equatorial orientation, as indicated by the observed large axial–axial coupling constants of the protons at C-2′.[14]

The conformations of the two sulfoxide stereoisomers (**9** and **10**) are influenced by the preference of the sulfinyl oxygen for the axial orientation.[15] The large axial–axial coupling constant of the 3′ proton in compound **9** indicates a high preference of the 5-fluorouracil group for the equatorial orientation (in both acetone-d_6 and Me_2SO-d_6), in contrast to the sulfide (**8**) in which this group is preferentially oriented axially. The available data do not permit an assignment of a preferred conformation in the other sulfoxide diastereoisomer (**10**). It is likely, however, that this diastereoisomer exists as an equilibrium mixture of conformations. The ^1H NMR spectrum of the unsaturated analogue **11** gives an AA′XX′ pattern for the OCH_2CH_2S fragment, indicating a rapid interconversion of equivalent conformations. The N and L parameters of 9 and 4.4 Hz, respectively, are virtually identical with those found in the case of oxathiene,[11b] which are 9 and 4.6 Hz.

The UV spectra of all of the pyrimidines analogues reported here are consistent with substitution at the N-1 position.[16]

Biological Evaluation. The effects of the various pyrimidine derivatives synthesized in the present study on in vitro tumor-cell growth are summarized in Table I. In addition, Table I shows the in vitro biological activity of 5-FUra, which was measured in every experiment with each cell line, and of Ftorafur using the L1210 cell line. All of the present derivatives are at least 100-fold less active than 5-FUra. Highest activities were observed for analogues **11** and **17** with the human erythroleukemia cell line (K-562); the compounds are approximately 100 and 200 times less active, respectively, than 5-FUra. Interestingly, all of the 1,4-dithiane analogues (**15–17**) show slight activity with the L1210 cell line, although this activity is approximately 1000-fold less than that for 5-FUra. Slight activity was also observed for analogue **15** with the MDAY-D2 cell line; the compound was approximately 2500-fold less active than 5-FUra.

Previous in vitro studies by Horwitz et al.[17] showed that the clinically useful drug Ftorafur was 30-fold less active than 5-FUra in inhibiting the growth of human fibroblasts. Since many of the 5-FUra analogues appear to function as relatively nontoxic and slowly releasing reservoirs of 5-FUra,[3c,g,4] the in vitro biological activities are much lower than the activities of the in vivo transformed compounds.[3g,17] In the case of Ftorafur, this transformation probably occurs in the liver microsomes.[4b] Studies are currently in progress to evaluate possible metabolic activation of the present analogues to more active compounds.

Experimental Section

Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ^1H NMR spectra were determined with either a Bruker CXP-200 or a Varian EM-360 spectrometer. The proton chemical shifts are given relative to Me_4Si (δ 0). The ^{19}F NMR spectra were determined with a Bruker CXP-200 spectrometer. The fluorine chemical shifts are given relative to external $CFCl_3$ (δ 0). The IR spectra were recorded with a Perkin-Elmer 598 infrared spectrophotometer and the UV spectra with a Perkin-Elmer 552 spectrophotometer. TLC was performed using silica gel 60 F-254 purchased from BDH Chemicals. The developed plates were sprayed with 1% ceric sulfate and 1.5% molybdic acid in 10% aqueous sulfuric acid and heated at about 150 °C.

Pummerer Reaction with 1,4-Oxathiane 4-Oxide (2). A solution of 1,4-oxathiane 4-oxide[20] (**2**; 6.6 g, 55 mmol) in toluene (80 mL) containing acetic anhydride (7.4 mL) and p-toluenesulfonic acid monohydrate (~10 mg) was heated at reflux temperature for 3 h. The solution was washed with aqueous $NaHCO_3$ (4 × 30 mL) and water (30 mL) and then dried over $MgSO_4$. The solvent volume was reduced to 10 mL, and the three components which in TLC [2:5 (v/v) ethyl acetate–petroleum ether (bp 35–60 °C)] had R_f 0.77, 0.54, and 0.43 were separated by silica gel column chromatography. The fastest-moving component (0.84 g, 15%) was identified by ^1H NMR[11b] as 1,4-oxathiene (**4**). The component (0.50 g, 5.6%) having R_f 0.54 was identified by ^1H NMR as 2-acetoxy-1,4-oxathiane (**5**): ^1H NMR ($CDCl_3$) δ 2.13 (3 H, s, OAc), 2.4–3.1 (4 H, H_2CSCH_2), 3.7–4.5 (2 H, OCH_2), 5.8–6.0 (1 H, m, H-2). The slowest-moving component (0.40 g, 4.4%) was identified by ^1H NMR as 3-acetoxy-1,4-oxathiane (**3**): ^1H NMR ($CDCl_3$) δ 2.17 (3 H, s, OAc), 2.3 (1 H, br d, H-5e), 3.3 (1 H, t of d, H-5a), 3.6–4.3 (4 H, H_2COCH_2), 5.5 (1 H, br s, H-3).

1-(1,4-Oxathian-3-yl)-5-fluorouracil (8). A mixture containing 0.701 g (4.32 mmol) of 3-acetoxy-1,4-oxathiane (**3**) and 0.562 g (4.32 mmol) of 5-fluorouracil in 50 mL of absolute acetonitrile was cooled to ice-bath temperature. To this mixture were added 0.8 equiv of TCS and 0.8 equiv of HMDS.[1] To this stirred mixture was added 1.2 equiv of $SnCl_4$ in 10 mL of absolute acetonitrile over a period of 10 min. The reaction solution was

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stirred for an additional 30 min at ice-bath temperature. The reaction solution was then diluted with CH_2Cl_2 (150 mL), extracted with aqueous $NaHCO_3$ (30 mL), followed by H_2O (15 mL), and then dried over Na_2SO_4. Evaporation of solvent gave a pale-yellow solid (1.12 g), which was dissolved in hot ethyl acetate (50 mL); crystallization was induced by the addition of petroleum ether (bp 35–60 °C) to give 0.825 g (82%) of a white solid (**8**), which was revealed by TLC [1:1 (v/v) petroleum ether–ethyl acetate] to consist of a single component having R_f 0.23; mp 185–186 °C; UV λ_{max} (C_2H_5OH) 211 nm (ϵ 8460), 274 (9350); λ_{max} (0.01 N HCl in C_2H_5OH) 211 nm (ϵ 8500), 274 (9320); λ_{max} (0.01 N NaOH in C_2H_5OH) 218 nm (ϵ 8590), 273 (7480); ^1H NMR (acetone-d_6, 300 K, 200 MHz)[21] δ 2.62 (1 H, d of m, J_{gem} = 14.1 Hz, $^3J_{ee}$ = 3.8 Hz, $^3J_{ea}$ = 2.6 Hz, $^4J_{3'}$ = 0.7 Hz, H-5'e), 3.24 (1 H, m, J_{gem} = 14.1 Hz, $^3J_{aa}$ = 10.1 Hz, $^3J_{ae}$ = 3.4 Hz, H-5'a), 3.88 (1 H, m, J_{gem} = 11.9 Hz, $^3J_{aa}$ = 10.1 Hz, $^3J_{ae}$ = 2.6 Hz, H-6'a), 4.20 (1 H, d of d, J_{gem} = 13.2 Hz, $^3J_{ae}$ = 3.3 Hz, H-2'a), 4.21 (1 H, m, J_{gem} = 11.9 Hz, $^3J_{ee}$ = 3.8 Hz, $^3J_{ea}$ = 3.4 Hz, H-6'e), 4.35 (1 H, d of d, J_{gem} = 13.2 Hz, $^3J_{ee}$ = 3.3 Hz, H-2'e), 5.34 (1 H, m, $^3J_{ee}$ = 3.3 Hz, $^3J_{ea}$ = 3.3 Hz, $^4J_{5'e}$ = 0.7 Hz, H-3'e), 8.36 (1 H, d, J = 7.0 Hz, CH=CF), 10.5 (br s, CONHCO); ^{19}F NMR δ −102 (d, J = 7.3 Hz, CH=CF). Anal. ($C_8H_9N_2O_3SF$) C, H, N, S, F.

1-(4-Oxo-1,4-oxathian-3-yl)-5-fluorouracil (9 and 10). To 0.88 g (3.8 mmol) of compound **8** suspended in H_2O (50 mL) at ice-bath temperature was added 0.82 g (3.8 mmol) of $NaIO_4$ in H_2O (50 mL), and the suspension was stirred for 10 h at room temperature. The volume was then reduced to 15 mL on a rotary evaporator, the mixture was cooled to ice-bath temperature, and the white solid was collected by filtration and washed once with cold H_2O and twice with cold CH_3OH to give 0.71 g (76%) of white crystals, which were revealed by TLC [3:1 (v/v) ethyl acetate–2-butanone] to consist of two components having R_f 0.37 (**9**) and 0.27 (**10**). The components were separated by silica gel column chromatography and recrystallized from water. Compound **9** (R_f 0.37) had mp 275–276 °C dec; UV λ_{max} (C_2H_5OH) 207 nm (ϵ 9440), 272 (9440); λ_{max} (0.01 N HCl in C_2H_5OH) 210 nm (ϵ 9310), 272 (9720); λ_{max} (0.01 N NaOH in C_2H_5OH) 231 nm (ϵ 9600), 271 (7790); ^1H NMR (Me_2SO-d_6, 300 K, 200 MHz) δ 3.02 (1 H, br d, J_{gem} = 14.5 Hz, $^3J_{ee}$ = 2.4 Hz, $^3J_{ea}$ = 1.7 Hz, H-5'e), 3.31 (1 H, m, J_{gem} = 14.5 Hz, $^3J_{aa}$ = 11.8 Hz, $^3J_{ae}$ = 4.1 Hz, H-5'a), 3.89 (1 H, m, J_{gem} = 12.5 Hz, $^3J_{ea}$ = 4.1 Hz, $^3J_{ee}$ = 2.4 Hz, H-6'e), 3.91 (1 H, d of d, J_{gem} = 12.0 Hz, $^3J_{ea}$ = 4.1 Hz, H-2'e), 4.05 (1 H, t of d, J_{gem} = 12.5 Hz, $^3J_{aa}$ = 11.8 Hz, J_{ae} = 1.7 Hz, H-6'a), 4.42 (1 H, d of d, J_{gem} = 12.0 Hz, $^3J_{aa}$ = 10.7 Hz, H-2'a), 5.45 (1 H, m, $^3J_{aa}$ = 10.7 Hz, $^3J_{ae}$ = 4.1 Hz, J = 1.1 Hz, H-3'a), 7.84 (1 H, d, J = 7.0 Hz, CH=CF), 12.07 (1 H, br s, CONHCO); ^{19}F NMR δ −167 (d, J = 7.3 Hz, CH=CF). Anal. ($C_8H_9N_2O_4SF$) C, H, N, S, F. Compound **10** (R_f 0.27) had mp 292–293 °C dec; UV λ_{max} (C_2H_5OH) 207 nm (ϵ 8650), 272 (8690); λ_{max} (0.01 N HCl in C_2H_5OH) 210 nm (ϵ 8770), 272 (9050); λ_{max} (0.01 N NaOH in C_2H_5OH) 220 nm (ϵ 7550), 234 (8360), 271 (7210); ^1H NMR (Me_2SO-d_6, 300 K, 200 MHz) δ 2.93 (1 H, m, J_{gem} = 13.6 Hz, $^3J_{aa}$ = 8.3 Hz, $^3J_{ae}$ = 2.9 Hz, H-5'a), 3.47 (1 H, m, J_{gem} = 13.6 Hz, $^3J_{ee}$ = 6.6 Hz, $^3J_{ea}$ = 2.6 Hz, H-5'e), 3.71 (1 H, m, J_{gem} = 12.9 Hz, $^3J_{aa}$ = 8.3 Hz, $^3J_{ae}$ = 2.6 Hz, H-6'a), 4.08 (1 H, d of d, J_{gem} = 13.2 Hz, $^3J_{ae}$ = 7.0 Hz, H-2'a), 4.13 (1 H, m, J_{gem} = 12.9 Hz, $^3J_{ee}$ = 6.6 Hz, $^3J_{ea}$ = 2.9 Hz, H-6'e), 4.32 (1 H, d of d, J_{gem} = 13.2 Hz, $^3J_{ee}$ = 3.7 Hz, H-2'e), 4.93 (1 H, d of d, $^3J_{ea}$ = 7.0 Hz, $^3J_{ee}$ = 3.7 Hz, H-3'), 8.24 (1 H, d, J = 7.0 Hz, CH=CF), 12.07 (1 H, br s, CONHCO); ^{19}F NMR δ −166 (d, J = 7.3 Hz, CH=CF). Anal. ($C_8H_9N_2O_4SF$) C, H, N, S, F.

1-(1,4-Oxathien-3-yl)-5-fluorouracil (11). A solution of **10** (0.299 g, 1.20 mmol) in acetic anhydride (60 mL) was stirred under N_2 at 115 °C for 10.5 h. The acetic anhydride was removed by distillation at reduced pressure to give a white solid, which was shown by TLC [6:1 (v/v) ethyl acetate–toluene] to consist of five components having R_f 0.75, 0.59, 0.30, 0.18, and 0.11. Fractionation on a silica gel column afforded the three components having R_f 0.59, 0.18, and 0.11. The component having R_f 0.11, a value corresponding to that of the starting material (**10**), was obtained in a yield of 15 mg after recrystallization from water. The component having R_f 0.18 was obtained in a yield of 29 mg from the column and recrystallized from water to afford 15 mg of compound **9**. The component (100 mg) having R_f 0.59 was recrystallized from methanol–petroleum ether (bp 35–60 °C) to give compound **11**: yield 67 mg (24%); mp 275–278 °C dec; UV λ_{max} (C_2H_5OH) 210 nm (ϵ 10 300), 265 (8910); λ_{max} (0.01 N HCl in C_2H_5OH) 211 nm (ϵ 10 300), 266 (9070); λ_{max} (0.01 N NaOH in C_2H_5OH) 231 nm (ϵ 12 300), 265 (7050); ^1H NMR (acetone-d_6, 300 K, 200 MHz) δ 3.19 (2 H, XX' part of an AA'XX' pattern, ΔJ_{gem} = 2.1 Hz, N = 9.0 Hz, L = 4.4 Hz, CH_2S), 4.34 (2 H, AA' part of AA'XX' pattern, CH_2O), 7.09 (1 H, s, H-2'), 7.73 (1 H, d, J = 6.2 Hz, CH=CF), 10.4 (br s, CONHCO); ^{19}F NMR δ −100 (d, J = 6.1 Hz, CH=CF). Anal. ($C_8H_7N_2O_3SF$) C, H, N, S, F.

1-(1,4-Oxathian-2-yl)-5-fluorouracil (12). The procedure employed for coupling 2-acetoxy-1,4-oxathiane (**4**; 0.513 g, 3.16 mmol) with 5-fluorouracil (0.411 g, 3.16 mmol) was identical with that used for preparing **8**. Evaporation of the solvent gave 0.866 g of a white solid, which was recrystallized from H_2O to give 0.476 g (65%) of **12**: TLC R_f 0.32 [1:1 (v/v) petroleum ether (bp 35–60 °C)–ethyl acetate]; mp 216 °C; UV λ_{max} (C_2H_5OH) 205 nm (ϵ 9810), 268 (9390); λ_{max} (0.01 N HCl in C_2H_5OH) 206 nm (ϵ 9800), 268 (9400); λ_{max} (0.01 N NaOH in C_2H_5OH) 217 nm (ϵ 8000), 267 (7100); ^1H NMR (acetone-d_6, 300 K, 200 MHz) δ 2.38 (1 H, d of q, J_{gem} = 13.8 Hz, $^3J_{ea}$ = 2.1 Hz, $^3J_{ee}$ = 2.1 Hz, $^4J_{3'e}$ = 2.1 Hz, H-5'e), 2.64 (1 H, d of m, J_{gem} = 13.2 Hz, $^3J_{ea}$ = 2.1 Hz, $^4J_{5'e}$ = 2.1 Hz, $^5J_{6'e}$ = 0.7 Hz, H-3'e), 2.91 (1 H, m, J_{gem} = 13.8 Hz, $^3J_{aa}$ = 11.7 Hz, $^3J_{ae}$ = 3.4 Hz, H-5'a), 3.08 (1 H, d of d, J_{gem} = 13.2 Hz, $^3J_{aa}$ = 10.3 Hz, H-3'a), 4.02 (1 H, m, J_{gem} = 12.0 Hz, $^3J_{aa}$ = 11.7 Hz, $^3J_{ae}$ = 2.1 Hz, H-6'a), 4.44 (1 H, d of m, J_{gem} = 12.0 Hz, $^3J_{ea}$ = 3.4, $^3J_{ee}$ = 2.1 Hz, $^5J_{3'e}$ = 0.7 Hz, H-6'e), 5.73 (1 H, d of t, $^3J_{aa}$ = 10.3 Hz, $^3J_{ae}$ = 2.1 Hz, J = 1.8 Hz, H-2'a), 7.85 (1 H, d, J = 7.0 Hz, CH=CF), 10.5 (br s, CONHCO); ^{19}F NMR δ −102 (br d, J = 6.1 Hz, CH=CF). Anal. ($C_8H_9N_2O_3SF$) C, H, N, S, F.

2-(Benzoyloxy)-1,4-dithiane (14). Benzoyl peroxide (12.3 g, 50.7 mmol) in benzene (60 mL) was added over a period of 80 min to a refluxing solution containing 14.6 g (121 mmol) of 1,4-dithiane (**13**) and 0.1 g (1 mmol) of CuCl in benzene (90 mL). The reaction mixture was kept in the cold room overnight (4 °C); it was diluted then with diethyl ether (200 mL) and extracted with aqueous Na_2CO_3 (4 × 30 mL) and H_2O (2 × 30 mL). The volume of the organic layer was reduced to ~100 mL on a rotary evaporator; an equal volume of ethanol was added, and the volume of this solution was reduced to ~100 mL. The 1,4-dithiane that precipitated was removed by filtration, the filtrate was evaporated, and the residue was recrystallized from ethanol; an additonal quantity of 1,4-dithiane was removed by sublimation. another recrystallization from ethanol afforded 3.18 g of product, which was revealed by TLC still to contain traces of impurities: ^1H NMR ($CDCl_3$) δ 2.5–3.7 (6 H, SCH_2), 5.9–6.1 (1 H, m, $W_{1/2}$ = 10 Hz, H-2'), 7.2–8.3 (5 H, Ar).

1-(1,4-Dithian-2-yl)-5-fluorouracil (15). The procedure for coupling 2-(benzoyloxy)-1,4-dithiane (**14**; 1.105 g, 4.60 mmol) with 5-fluorouracil (0.598 g, 4.60 mmol) was identical with that used for preparing **8**, except that after the catalyst had been added, the ice-bath was removed and the reaction mixture was stirred for 2 h at room temperature. Evaporation of solvent gave 1.37 g of a white solid, which was recrystallized from methanol to give **15**: yield 0.931 g (82%): TLC R_f 0.39 [1:1 (v/v) petroleum ether (bp 35–60 °C)–ethyl acetate]; mp 231–233 °C dec; UV λ_{max} (C_2H_5OH) 210 nm (ϵ 9350), 273 (9980); λ_{max} (0.01 N HCl in C_2H_5OH) 210 nm (ϵ 9530), 273 (9990); λ_{max} (0.01 N NaOH in C_2H_5OH) 217 nm (ϵ 9460), 272 (7790); ^1H NMR (acetone-d_6, 300 K, 200 MHz) δ 2.8–3.0 (2 H, H-5'e, H-5'a), 3.08 (1 H, d of d, J_{gem} = 13.6 Hz, $^3J_{ea}$ = 2.8 Hz, H-3'e), 3.18–3.39 (2 H,H-6'a, H-6'e), 3.42 (1 H, d of d, J_{gem} = 13.6 Hz, $^3J_{aa}$ = 9.8 Hz, H-3'a), 5.80 (1 H, m, $^3J_{aa}$ = 9.8 Hz, $^3J_{ae}$ = 2.8 Hz, J = 1.5 Hz, H-2'a), 7.99 (1 H, d, J = 7.0 Hz, CH=CF), 10.48 (br s, CONHCO); ^{19}F NMR δ −98 (br d, J = 6.1 Hz, CH=CF). Anal. ($C_8H_9N_2O_2S_2F$) C, H, N, S, F.

1-(1,4-Dithian-2-yl)uracil (16). The procedure for coupling 2-(benzoyloxy)-1,4-dithiane (**14**; 0.417 g, 1.74 mmol) with uracil (0.195 g, 1.74 mmol) was identical with that used for preparing **15**. Evaporation of the solvent gave a white solid (0.58 g), which was recrystallized from CH_3OH to give **16**: yield 0.24 g (59%); TLC R_f 0.18 [1:1 (v/v) petroleum ether (bp 35–60 °C)–ethyl acetate]; mp 223–226 °C dec; UV λ_{max} (C_2H_5OH) 209 nm (ϵ 9540), 265 (11 100); λ_{max} (0.01 N HCl in C_2H_5OH) 209 nm (ϵ 9730), 265

(21) The coupling constants given here are the observed coupling constants which are the time-averaged coupling constants of different conformers (see ref 13).

(11 000); λ_{max} (0.01 N NaOH in C_2H_5OH) 217 nm (ϵ 9230), 265 (8530); ^1H NMR (acetone-d_6, 300 K, 200 MHz) δ 2.8–3.0 (2 H, H-5'a, H-5'e), 3.07 (1 H, d of d, J_{gem} = 13.6 Hz, $^3J_{ea}$ = 2.8 Hz, H-3'e), 3.15–3.35 (2 H, H-6'a, H-6'e), 3.37 (1 H, d of d, J_{gem} = 13.6 Hz, $^3J_{aa}$ = 9.8, H-3'a), 5.65 (1 H, d, J_{H-6} = 8.2 Hz, H-5), 5.80 (1 H, d of d, $^3J_{aa}$ = 9.8 Hz, $^3J_{ae}$ = 2.8 Hz, H-2'a), 7.78 (1 H, d, J_{H-5} = 8.1 Hz, H-6), 10 (br s, CONHCO). Anal. ($C_8H_{10}N_2O_2S_2$) C, H, N; S: calcd, 27.84; found, 26.57.

1-(1,4-Dithian-2-yl)thymine (17). The procedure for coupling 2-(benzoyloxy)-1,4-dithiane (**14**; 0.441 g, 1.83 mmol) with thymine (0.231 g, 1.83 mmol) was identical with that used for preparing **15**. Evaporation of the solvent gave a white solid (0.56 g), which was recrystallized from CH_3OH to give **17**: yield 0.30 g (67%); TLC R_f 0.33 [1:1 (v/v) petroleum ether (bp 35–60 °C)–ethyl acetate]; mp 217–218 °C; UV λ_{max} (C_2H_5OH) 212 nm (ϵ 9590), 270 (11 000); λ_{max} (0.01 N HCl in C_2H_5OH) 212 nm (ϵ 9680), 270 (10 900); λ_{max} (0.01 N NaOH in C_2H_5OH) 218 nm (ϵ 10 500), 270 (8580); ^1H NMR (acetone-d_6, 300 K, 200 MHz) δ 1.85 (3 H, d, $^4J_{H-6}$ = 1.2 Hz, CH_3), 2.8–3.0 (2 H, H-5'a, H-5'e), 3.0 (1 H, d of d, J_{gem} = 13.4 Hz, $^3J_{ea}$ = 2.6 Hz, H-3'e), 3.14–3.25 (1 H, d of t, J_{gem} = 14.0 Hz, ^3J = 4.0 Hz, H-6'e), 3.27–3.40 (1 H, m, J_{gem} = 14.0 Hz, $^3J_{aa}$ = 8.6 Hz, $^3J_{ae}$ = 4.6 Hz, H-6'a), 3.41 (1 H, d of d, J_{gem} = 13.4 Hz, $^3J_{aa}$ = 10.4 Hz, H-3'a), 5.81 (1 H, d of d, $^3J_{aa}$ = 10.4 Hz, $^3J_{ae}$ = 2.6 Hz, H-2'), 7.58 (1 H, quartet, $^4J_{CH_3}$ = 1.2 Hz, H-6), 10.03 (br s, CONHCO). Anal. ($C_9H_{12}N_2O_2S_2$) C, H, N; S: calcd, 26.25; found, 25.02.

1-(1,4-Dioxan-2-yl)-5-fluorouracil (20). The procedure for coupling 2-(benzoyloxy)-1,4-dioxane[10] (**19**; 1.11 g, 5.35 mmol) with 5-fluorouracil (0.70 g, 5.35 mmol) was identical with that used for preparing **8**. Evaporation of the solvent gave a white solid (1.78 g), which was recrystallized from methanol to give **20**: yield 0.81 g (70%); TLC R_f 0.16 [1:1 (v/v) petroleum ether (bp 35–60 °C)–ethyl acetate]; mp 217 °C; UV λ_{max} (C_2H_5OH) 207 nm (ϵ 8480) 267 (8560); λ_{max} (0.01 N HCl in C_2H_5OH) 207 nm (ϵ 8490), 267 (8540); λ_{max} (0.01 N NaOH in C_2H_5OH) 217 nm (ϵ 7700), 266 (6300); ^1H NMR (acetone-d_6, 300 K, 200 MHz) δ 3.6–3.8 (2 H, H-5'e, H-5'a), 3.63 (1 H, d of d, J_{gem} = 11.4 Hz, $^3J_{aa}$ = 8.8 Hz, H-3'a), 3.85–3.97 (1 H, t of d, H-6'a), 3.90 (1 H, d of d, J_{gem} = 11.4 Hz, $^3J_{ea}$ = 3.3 Hz, H-3'e), 3.99–4.07 (1 H, d of t, H-6'e), 5.68 (1 H, m, $^3J_{aa}$ = 8.8 Hz, $^3J_{ae}$ = 3.3 Hz, ^5J_F = 1.7 Hz, H-2'a), 7.92 (1 H, d, J = 7.0 Hz, CH=CF), 10.49 (br s, CONHCO); ^{19}F NMR δ −99, (d of d, $J_{CH=CF}$ = 7.0 Hz, $^5J_{2'a}$ = 1.6 Hz, CH=CF). Anal. ($C_8H_9N_2O_4F$) C, H, N, F.

Screening for Biological Activity Using Cell Cultures. All cell-growth experiments were performed using plastic plates containing 24 wells, 16 mm in diameter (2.0-cm^2 surface area). The medium for the MDAY-D2 cells was Alpha MEM (Gibco, Grand Island, NY) and for the L1210 and K-562 it was RPMI 1640 (Gibco). All media contained 10% fetal calf serum (Flow Laboratories, Rockville, MD) and antibiotics (penicillin and streptomycin).[22]

Compounds tested for biological activity were dissolved in Me_2SO and then diluted with the above media to give the desired concentrations. The cells used for screening were suspended in fresh medium at a concentration of 10^3–10^4 cells per milliliter; 1 mL of this cell suspension was added to each well. On the following day the test compounds were added to the cells in 1 mL of medium. Two wells of cells were used for each concentration of the test compound. Each of the controls received 1 mL of medium containing 1% Me_2SO, so that all cultures contained a final concentration of 0.5% of Me_2SO by volume. Cells in two of the control wells were counted each day (using a Coulter counter) to monitor the growth of the cells. In 5–6 days after the addition of the test compounds or just before the control cultures had attained their maximal cell densities, the cells in each well were counted.

ID_{50}'s were obtained from log–log plots of the compound concentration vs. cell numbers at the end of the incubation period, the cell numbers of the control cultures being taken as 100% (see also Table I).

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(22) The media used was kindly prepared by Mrs. Majka Florian.

Isomeric Cyclopropyl Ring-Methylated Homologues of *trans*-2-(2,5-Dimethoxy-4-methylphenyl)cyclopropylamine, an Hallucinogen Analogue

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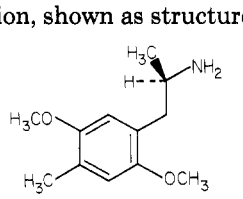
The hallucinogen analogue *trans*-2-(2,5-dimethoxy-4-methylphenyl)cyclopropylamine was modified by adding a 3-methyl group, either cis or trans with respect to the amino group. These two isomeric cyclopropyl ring-methylated compounds were then tested for activity in the mouse ear-scratch assay and for a contractile effect in the rat fundus preparation. Neither compound was found to possess appreciable activity when compared to the nonmethylated parent, in either assay.

A large number of substituted phenethylamine derivatives have been synthesized and evaluated for hallucinogen-like biological activity. One of the more well known and studied of these, 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane, (DOM, STP), is quite potent, and the more active enantiomer has the *R* absolute configuration, shown as structure **1**. Surprisingly, extension of the α-methyl of **1** to the α-ethyl homologue **2** abolishes hallucinogenic activity.[1] The ethyl congener **2** also lacks potency, relative to **1**, in a number of other biological assays.[2-4] No satisfactory explanation for the difference in



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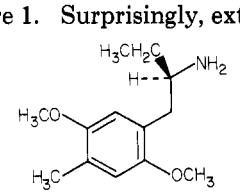

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