Acknowledgments.—The authors are indebted to Dr. Peter Lim for the infrared interpretations and to his staff for the spectral data and paper chromatography. The authors also thank Dr. Lois Durham of Stanford University for some of the nmr interpretations.

Compounds Derived from L-Threitol 1,4-Bismethanesulfonate

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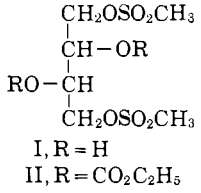
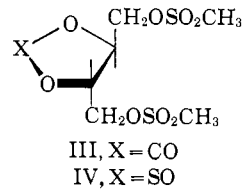
In continuation of the synthesis of the 1,4-bismethanesulfonates of the stereoisomeric butanetetraols and related compounds,[1] and for reasons already discussed[1] we prepared the following derivatives of L-threitol 1,4-bismethanesulfonate (I) with the purpose of obtaining substances for investigation as anticancer agents, and of getting further information about the structure–activity relationship of this type of alkylating agents: di-2,3-*O*-carbethoxy-L-threitol 1,4-bismethanesulfonate (II), the 2,3-cyclic carbonate of I (III) [L-4,5-bismethylsulfonyloxymethyl-1,3-dioxolanone-(2)], and the 2,3-cyclic sulfite of I (IV) (L-4,5-bismethylsulfonyloxymethyl-1,3,2-dioxathiolane 2-oxide). The compounds were obtained by reaction of I with ethyl chloroformate, phosgene, and thionyl chloride, respectively.



I, R = H
II, R = $CO_2C_2H_5$



III, X = CO
IV, X = SO

Screening by the Cancer Chemotherapy National Service Center, National Institutes of Health, has revealed no significant difference in antineoplastic activity between these derivatives and that of I,[2] as far as the Walker carcinosarcoma 256 system is concerned. Moreover, in the KB cell culture system the ED_{50} determined for II is more than ten times as high as that of I, III, and IV. A summary of the test data is presented in Tables I and II.

TABLE I

SCREENING DATA IN THE WALKER CARCINOSARCOMA 256 (SUBCUTANEOUS) SYSTEM

Compd	Daily dose, mg/kg[a]	Survivors	Mean tumor weight test/control, %[b]	ED_{90},[c] mg/kg/day
II	200	6/6	0	
	100	6/6	6	120
	50	6/6	95	
	25	6/6	75	
III	200	6/6	0	
	100	6/6	47	130
	50	6/6	70	
	25	6/6	92	
IV	200	6/6	0	
	100	6/6	17	130
	50	6/6	48	
	25	6/6	105	

[a] Administered ip once daily, days 1 through 5 postinoculation. [b] Sacrificed and evaluated 10 days postinoculation. [c] The dose that inhibits growth to 10% of control growth.

TABLE II

SCREENING DATA IN THE KB CELL CULTURE SYSTEM

Compd	ED_{50},[a] μg/ml	Slope[b]
I[c]	5.0	−0.43
	11	−0.56
	3.6	−0.28
II	>100	
III	7.2	−0.54
IV	9.8	−0.55

[a] The dose that inhibits growth to 50% of control growth. [b] Change of response for each 1 log change of dose. [c] Tested at different days.

Experimental Section[3]

Di-2,3-*O*-carbethoxy-L-threitol 1,4-Bismethanesulfonate (II).—To a solution of L-threitol 1,4-bismethanesulfonate (10 g) in pyridine (50 ml), ethyl chloroformate (8 ml) was added dropwise while stirring at 0 to 5°. The mixture was stirred for additional 30 min, kept in a refrigerator for 40 hr, and then poured into 4 *N* HCl (100 ml) while cooling. The separated oil was extracted with chloroform, the organic layer was washed several times with water, and after drying ($MgSO_4$) the solvent was removed by evaporation *in vacuo*. The residue was triturated with diethyl ether, and the resulting crystalline material (12.7 g) was recrystallized from benzene–diethyl ether (decolorizing carbon) yielding II (10.2 g) with mp 58–61°. The analytically pure compound was reached by filtration of a solution of crude II in benzene through aluminum oxide (anionotropic, activity grade I), evaporating the filtrate *in vacuo*, and triturating the residue with a small amount of benzene, affording crystallization, followed by recrystallization from chloroform–diethyl ether, mp 62–64° (shrinking at 58°), $[\alpha]^{20}D$ −9.8° (*c* 2, acetone).

Anal. Calcd for $C_{12}H_{22}O_{12}S_2$: C, 34.12; H, 5.25; S, 15.18. Found: C, 34.17; H, 5.31; S, 15.15.

L-4,5-Bismethylsulfonyloxymethyl-1,3-dioxolanone-(2) (III).—To a solution of L-threitol 1,4-bismethanesulfonate (10 g) in pyridine (40 ml), a solution of phosgene (4.5 g) in diethyl ether (20 ml) was added dropwise while stirring at 0 to 5°. The reaction mixture was kept in a refrigerator for 70 hr and then poured into a mixture of 4 *N* HCl (100 ml) and ice. The solid (10.5 g) which separated was filtered off and recrystallized from acetone–diethyl ether (75 ml each) (decolorizing carbon), yielding crude III (7.9 g) with mp 123–125°. The analytically pure and colorless III was obtained by filtration of a warm solution of the crude material in acetone through aluminium oxide (anionotropic, activity grade I), and precipitation by adding diethyl ether to the filtrate, followed by recrystallization from a small amount of acetone, mp 126–127°, $[\alpha]^{20}D$ −62.6° (*c* 2, acetone).

Anal. Calcd for $C_7H_{12}O_9S_2$: S, 27.63; H, 3.98; S, 21.07. Found: C, 27.82; H, 4.19; S, 21.01.

L-4,5-Bismethylsulfonyloxymethyl-1,3,2-dioxathiolane 2-Oxide (IV).—A suspension of L-threitol 1,4-bismethanesulfonate (10 g) in $SOCl_2$ (25 ml) was refluxed for 45 min. After cooling, the obtained solution was evaporated to dryness *in vacuo*. The oily residue was treated with benzene (25 ml), and the evaporation was repeated. The crystalline residue was dissolved in ethyl acetate (200 ml); the solution was washed twice with water, dried ($MgSO_4$), and evaporated *in vacuo* to yield IV (11.5 g) with mp 97.5–99°. The crude material was recrystallized from ethyl acetate (50 ml) and redissolved in warm ethyl acetate (75 ml); the warm solution was diluted with diethyl ether (50 ml) and chilled after filtration over decolorizing carbon removing turbidity, mp 98.5–100°, $[\alpha]^{20}D$ −105.5° (*c* 2, acetone).

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(3) Analyses were by G. Cornali and W. Egger of these laboratories. Melting points were taken in open glass capillaries and rounded off to half degrees, using a Hershberg apparatus with thermometers subdivided in 0.1°. Technical assistance was by Th. Rolle.

Anal. Calcd for $C_6H_{12}O_9S_3$: C, 22.22; H, 3.73; S, 29.65. Found: C, 22.30; H, 3.80; S, 29.70.

Acknowledgment.—The author is indebted to the Cancer Chemotherapy National Service Center, National Institutes of Health, Bethesda 14, Maryland, for the screening of the compounds and for making the results available.

Synthesis of Grisan and Coumaran-3-one Derivatives with Potential Insect-Repellent Properties[1]

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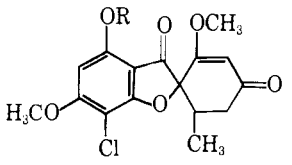
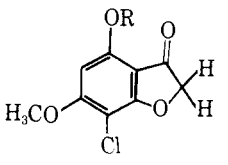
In developing structural designs for compounds which would prove effective as systemically administered insect repellents, we sought to combine within a *single molecule* (1) a component known to have affinity for dermal tissue with (2) a component possessing certain insect-repellent (or prophylactic or therapeutic) properties. In the initial phase of our exploratory work, we have synthesized a series of compounds (I–III and VI–VIII) combining into one molecular entity a moiety (IV) known to be transported to and found in epidermal tissue in significant quantities[2] [or a component (IX) of the latter], with moieties ascertained to have mosquito-repellent properties (anisyl alcohol,[3a] N,N-diethyl-*m*-toluamide,[3b] and citronellol[3c]).





I, R = *p*-$CH_2C_6H_4OCH_3$
II, R = *m*-$CH_2C_6H_4CON(C_2H_5)_2$
III, R = $CH_2CH_2CH(CH_3)CH_2CH_2CH{=}C(CH_3)_2$
IV, R = CH_3
V, R = H

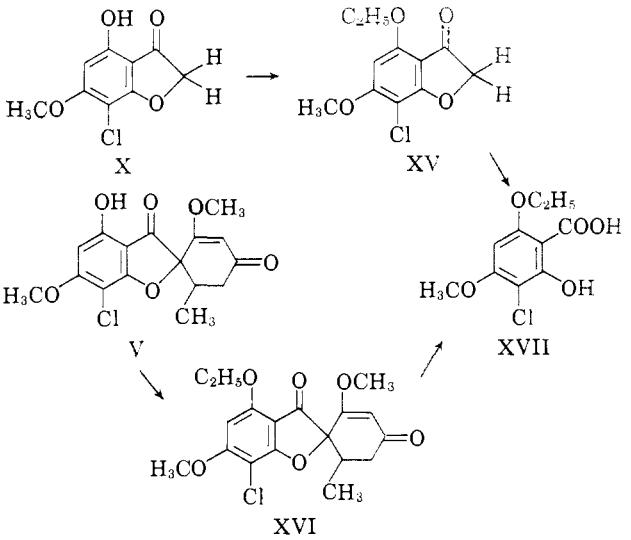
VI, R = *p*-$CH_2C_6H_4OCH_3$
VII, R = *m*-$CH_2C_6H_4CON(C_2H_5)_2$
VIII, R = $CH_2CH_2CH(CH_3)CH_2CH_2CH{=}C(CH_3)_2$
IX, R = CH_3
X, R = H

Chemistry.—The subject compounds could be viewed, basically, as condensation products of 4-demethylgriseofulvin[4] (V) and of the corresponding coumaran-3-one (X) with anisyl alcohol, N,N-diethyl-*m*-toluamide, and citronellol.

Compounds I, II, and III were actually obtained by treating V with anisyl bromide[5] (XI), 3-(N,N-diethylcarbamoyl)benzyl bromide (XII), and citronellyl bromide[6] (XIII) in acetone and/or dimethylformamide, in the presence of potassium carbonate.

7-Chloro-4-hydroxy-6-methoxycoumaran-3-one (X), a hitherto unreported moiety, was obtained by the selective demethylation of 7-chloro-4,6-dimethoxycoumaran-3-one (IX) using a modification of the procedure employed in the demethylation of griseofulvin by Arkley, *et al.*[4]

The structure of the hydroxycoumaranone (X) was established by chemical and spectral evidence. Oxidative degradation of X in anticipation of obtaining the known[7] 3-chloro-2,6-dihydroxy-4-methoxybenzoic acid proved unsuccessful. Our inability to isolate a product from this direct oxidation appears to be consistent with the observation of Molho[8]; according to his interpretation, the corresponding salicylic acid derivative could not be obtained from a 4-hydroxy-substituted coumaranone because it is destroyed under the prevailing reaction conditions. Since our attempts to oxidize 7-chloro-4,6-dimethoxycoumaran-3-one (IX) met with success and yielded the expected 3-chloro-2-hydroxy-4,6-dimethoxybenzoic acid[9] (XIV), we were led to the following approach. Both the hydroxycoumaranone (X) and the known[4] 7-chloro-4-hydroxy-6,2′-dimethoxy-6′-methylgris-2′-ene-3,4′-dione (V), upon conversion to the respective ethyl ether derivatives (XV and XVI[4]) and subsequent oxidation with potassium permanganate, yielded the same acid, 3-chloro-6-ethoxy-2-hydroxy-4-methoxybenzoic acid (XVII), as confirmed by the melting and mixture melting points of the acids as well as their superimposable infrared spectra, and the elemental analyses of the acid and its anilide derivative (XVIII). Moreover, had the hydroxycoumaranone been the isomeric 7-chloro-6-hydroxy-4-methoxycoumaran-3-one, oxidative degradation of its ethyl ether derivative would have afforded the known 3-chloro-4-ethoxy-2-hydroxy-6-methoxybenzoic acid,[10] mp 179–181° dec.



X XV V XVII XVI

(1) This investigation was supported by Research Contract No. DA-49-193-MD-2636 from the U. S. Army Medical Research and Development Command, Washington, D. C.

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