Acylthioxanthenes: Agents Which Selectively Reduce Decerebrate Rigidity in the Cat

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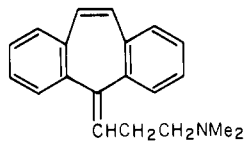
A series of 2-acylthioxanthene-$\Delta^{9(\gamma)}$-propylamines was synthesized, and their effect of reducing the intercollicular decerebrate rigidity in the cat was evaluated. The compound exhibiting the greatest separation between the dosage that reduced rigidity and that which caused sedation was (*Z*)-2-propionyl-9-[3-(dimethylamino)propylidene]thioxanthene. The separation of *Z* and *E* isomers was monitored by ^{1}H NMR spectroscopy, using an europium shift reagent.

A drug which reduces intercollicular decerebrate rigidity in the cat is considered to be of potential use in the treatment of patients with pyramidal spasticity.[1] Phenothiazines related to chlorpromazine (1) have been reported to possess such activity,[2] and dimethothiazine (2) has been shown to be of some value in man in this respect.[3] It is important, however, that the compound should have a negligible sedative effect, and initial studies in man indicated the need for a drug which was more potent than 2. In a series of 2-acyl-substituted phenothiazines it has been possible to separate, to a considerable extent, their potency in reducing decerebrate rigidity from their activity in tests of sedation,[4] and the most active compound, M&B 18706 (3), has been studied in detail.[1a,b] A similar pharmacological profile has also been demonstrated with the 2-acyl-8-chlorophenothiazine M&B 22079[5] (4).

1, Y = Cl; X = H; R = $(CH_2)_2NMe_2$
2, Y = SO_2NMe_2; X = H; R = $C(CH_3)HNMe_2$
3, Y = $CO(CH_2)_3CH_3$; X = H; R = $C(CH_3)HCH_2NMe_2$
4, Y = $COCH_3$; X = Cl; R = $C(CH_3)HCH_2NMe_2$
7, Y = $COCH_3$; X = H; R = $(CH_2)_2NMe_2$



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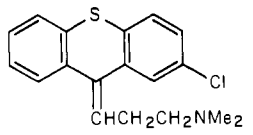

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Proheptatriene (5)[6] and chlorprothixene (6)[7] have also been shown to reduce intercollicular decerebrate rigidity in the cat. Structure–activity relationships in the thioxanthene and phenothiazine series of tricyclic compounds show many similar features. It was of interest, therefore, to examine 2-acylthioxanthenes for their ability to reduce rigidity and to find compounds whose potency, in this respect, was separated from their sedative properties.

The synthesis and pharmacological evaluation of acyl-substituted thioxanthene derivatives related to chlorprothixene are described. Included are data on some intermediate carbinols and a few saturated thioxanthene compounds (Tables V and VI).

Synthesis. The thioxanthene-$\Delta^{9(\gamma)}$-propylamines (**29–49**; Table IV) were prepared by the following methods. The 2-[(4-acylphenyl)thio]benzoic acid compounds (**8–14**; Table I) were prepared by the reaction of the appropriate thiosalicyclic acid with a 4-bromophenyl alkyl ketone[8] and on cyclodehydration with polyphosphoric acid (PPA) gave the corresponding acyl-substituted tricyclic ketones (**15–21**; Table II). The reaction of the tricyclic ketones with ethylene glycol and *p*-toluenesulfonic acid gave the monoketals (**22–28**; Table III) selectively. The tricyclic carbinols were prepared by the addition of a dialkylaminoalkylmagnesium chloride to the C-9 unprotected carbonyl group.[9] The majority of the carbinols were not isolated but were dehydrated using mineral acid in glacial acetic acid to yield the olefins (**29–49**; Table IV) as mixtures of the *Z* and *E* isomers. The mixtures were shown to contain approximately equal amounts of each isomer by ^{1}H NMR spectroscopy, and this ratio was confirmed by the addition of a europium-shift reagent. Compound **36** was, however, a 2:1 mixture of the *Z* and *E* isomers, respectively. The Experimental Section includes examples of such spectra. In the case of the more pharmacologically interesting olefins (**32**, **33**, and **35**; Table IV), the *Z* and *E* isomers were obtained by fractional crystallization. The separation was monitored by ^{1}H NMR spectroscopy, using an europium-shift reagent[10] (see Experimental Section).

The acyl-substituted carbinols (**50** and **54**; Table V) were obtained by removal of the ketal-protecting group with *p*-toluenesulfonic acid. The saturated thioxanthene derivatives (**51–53**; Table V) were prepared by catalytic reduction of the appropriate olefin.

Pharmacology. Results and Discussions. The compounds were administered intravenously in the initial tests in decerebrate cats. Those compounds, which exhibited high potency in these tests, together with a relative lack of sedative effects, as measured by the motor activity test in mice, were then examined for oral activity in reducing decerebrate rigidity. The results obtained with saturated thioxanthenes and some intermediate carbinols are given in Table VI.

Chlorpromazine (1) probably reduces the rigidity of the intercollicular decerebrate cat by depressing fusimotor

(1) (a) D. R. Maxwell, M. A. Read, and E. A. Sumpter, *Br. J. Pharmacol.*, **50**, 35 (1974). (b) D. R. Maxwell and E. A. Sumpter, *ibid.*, **50**, 355 (1974).
(2) E. M. Keary and D. R. Maxwell, *Br. J. Pharmacol. Chemother*, **30**, 400 (1976).
(3) D. Wheatley, *Practioner*, **213**, 101 (1974).
(4) S. C. Amin, D. H. Jones, and D. R. Maxwell, British Patent 1258005 (1971).
(5) S. C. Amin, Ger. Offen. 2241730 (1973); *Chem. Abstr.*, **78**, 147981*q* (1973).
(6) N. N. Share and C. S. McFarlane, *Pharmacologist*, **12**, 218 (1970).
(7) A. H. Loveless unpublished results.
(8) R. Raseanu, *Rev. Chim. (Bucharest)*, **20**, 659 (1969); *Chem. Abstr.*, **73**, 3752 (1970).
(9) C. Kaiser, A. M. Pavloff, E. Garvey, P. J. Fowler, D. H. Tedeschi, C. L. Zirkle, E. A. Nodiff, and A. J. Saggiomo, *J. Med. Chem.*, **15**, 665 (1972).
(10) (a) D. C. Remy and W. A. Van Saun, Jr., *Tetrahedron Lett.*, **27**, 2463 (1971); (b) C. Kaiser, R. J. Warren, and C. L. Zirkle, *J. Med. Chem.*, **17**, 131 (1974).

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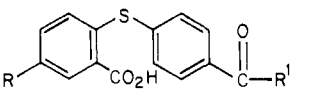
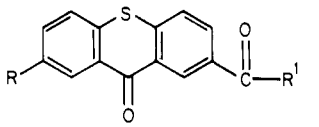
Table I. Compounds 8-14



no.	R	R^1	mp, °C	recrystn solvent	yield, %	formula[a]
8	H	CH_3	206-207[b]	MeOH	77	
9	H	CH_2CH_3	200-202	HOAc	66	$C_{16}H_{14}O_3S$
10	H	$CH(CH_3)_2$	152-155	EtOH	48	$C_{17}H_{16}O_3S$
11	H	$(CH_2)_2CH_3$	175-176	EtOH	75	$C_{17}H_{16}O_3S$
12	H	$(CH_2)_3CH_3$	128-130	Et_2O, pet. ether[c]	71	$C_{18}H_{18}O_3S$
13	Cl	CH_3	176-177[d]	EtOH	45	
14	Cl	CH_2CH_3	169-171	HOAc	40	$C_{16}H_{13}ClO_3S$

[a] All compounds were analyzed for C, H, and S, and the results were within 0.4% of theory. [b] Lit.[8] mp 205-206 °C. [c] Petroleum ether refers to fraction bp 40-60 °C. [d] Lit.[22] mp 179-181.5 °C.

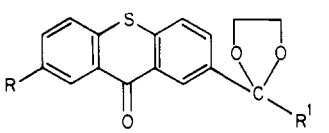
Table II. Compounds 15-21



no.	R	R^1	mp, °C	recrystn solvent	yield, %	formula[a]
15	H	CH_3	176-178[b]	EtOH	80	
16	H	CH_2CH_3	136-137	EtOH	72	$C_{16}H_{12}O_2S$
17	H	$CH(CH_3)_2$	144-145	EtOH	57	$C_{17}H_{14}O_2S$
18	H	$(CH_2)_2CH_3$	107-108	MeOH	65	$C_{17}H_{14}O_2S$
19	H	$(CH_2)_3CH_3$	104-105	EtOH	85	$C_{18}H_{16}O_2S$
20	Cl	CH_3	205-207[c]	EtOH	48	
21	Cl	CH_2CH_3	195-196	EtOAc/$CHCl_3$	20	$C_{16}H_{11}ClO_2S$

[a] See footnote a in Table I. [b] Lit.[8] mp 178-179 °C. [c] Lit.[22] mp 206-208 °C.

Table III. Compounds 22-28



no.	R	R^1	mp, °C	recrystn solvent	yield, %	formula[a]
22	H	CH_3	129-131	acetone-pet. ether[b]	62	$C_{17}H_{14}O_3S$
23	H	CH_2CH_3	124	EtOH	71	$C_{18}H_{16}O_3S$
24	H	$CH(CH_3)_2$	98-100	pet. ether[b]	68	$C_{19}H_{18}O_3S$
25	H	$(CH_2)_2CH_3$	80-82	pet. ether[b]	72	$C_{19}H_{18}O_3S$
26	H	$(CH_2)_3CH_3$	67-69	Et_2O-pet. ether[b]	16	$C_{20}H_{20}O_3S$
27	Cl	CH_3	159-161	EtOH	80	$C_{17}H_{13}ClO_3S$
28	Cl	CH_2CH_3	135-141	EtOH	80	$C_{18}H_{15}ClO_3S$

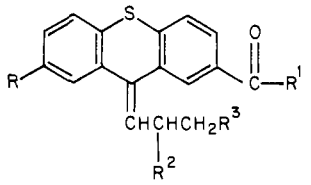
[a] See footnote a in Table I. [b] Petroleum ether refers to fraction bp 60-80 °C.

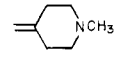
activity by an action at the supraspinal level.[11] Furthermore, it has been suggested that the potency of chlorpromazine (1), acepromazine (7), and other phenothiazine tricyclic compounds may be correlated with their ability in this respect to block peripheral α-adrenoreceptors.[1a] It has been postulated that 3 may reduce fusimotor activity and decerebrate rigidity by inhibiting receptors for noradrenaline in the CNS, while having little or no depressant action on receptors for dopamine.[1a] Thus, structural modification of acepromazine (7) in the phenothiazine series led to 3, which had a selectivity of action in respect of its activity in reducing decerebrate rigidity as compared to its sedative effect.

In intravenous tests in the decerebrate cat, the acetylthioxanthene (30) had a similar order of activity to that of chlorpromazine (1) and chlorprothixene (6) and was equipotent in the motor activity test. The propionyl-substituted compound (36) was more potent in reducing decerebrate rigidity and was less sedative. Further extension of the alkyl chain on the acyl group led to a loss of activity in both the decerebrate cat and the motor activity test. Compounds with a branched aminopropylidene side chain followed a similar pattern to that found with the unbranched side-chain compounds, the optimum activity (in the decerebrate cat with a relative lack of potency in the motor activity test) was again found with the propionyl derivative (34). The unbranched aminopropylidenethioxanthenes were more potent in reducing decerebrate rigidity than their branched-chain counterparts, although they were of similar potency in the test of sedation. The introduction of a chloro substituent into the 8 position of 2-acylphenothiazines led to a retention of potency in the decerebrate cat while maintaining the relative lack of sedative effects.[5] It was found, however, that the introduction of the chloro substituent required an alteration in the lipophilic nature of the acyl substituent,[5] optimum activity being achieved with the 2-acetyl-

(11) G. Busch, H. D. Henatsch, and F. J. Schulte, *Arzneim.-Forsch.*, **10**, 217 (1960).

Table IV. Aminopropylidene Derivatives of Thioxanthenes



no.	R^1	R	R^2	R^3	salt	mp, °C	yield, %	formula[a]
29	CH_3	H	CH_3	$N(CH_3)_2$	HCl[b]	220-227	82	$C_{21}H_{23}NOS$
30	CH_3	H	H	$N(CH_3)_2$	HCl[b]	226-228	81	$C_{20}H_{21}NOS$
31	CH_3	Cl	CH_3	$N(CH_3)_2$	HCl[b]	202-210	24	$C_{21}H_{22}ClNOS$
32[c]	CH_3	Cl	H	$N(CH_3)_2$	HCl	198-202	25	$C_{20}H_{20}ClNOS$
33[c]	CH_3	Cl	H	$N(CH_3)_2$	HCl	67-75	49	$C_{20}H_{20}ClNOS$
34	CH_2CH_3	H	CH_3	$N(CH_3)_2$	HCl	180-200	63	$C_{22}H_{25}NOS$
35[d]	CH_2CH_3	H	H	$N(CH_3)_2$	HCl[e]	210-213	73	$C_{21}H_{23}NOS$
36[f]	CH_2CH_3	H	H	$N(CH_3)_2$	HCl[g]	199-203	21	$C_{21}H_{23}NOS$
37	CH_2CH_3	H	CH_2CH_3	$N(CH_3)_2$	HCl[b]	194-196	89	$C_{23}H_{27}NOS$
38	CH_2CH_3	H	CH_3	c-$N(CH_2CH_2)_2O$	HCl[h]	97-104	42	$C_{24}H_{27}NO_2S$
39	CH_2CH_3	H	H	c-$N(CH_2CH_2)_2N$-CH_3	oxalate[g]	224-226	30	$C_{24}H_{28}NO_2S$
40	CH_2CH_3	H	H	c-$N(CH_2CH_2)_2O$	HCl[g]	101-105	65	$C_{23}H_{23}NOS$
41	CH_2CH_3	Cl	H	$N(CH_3)_2$	HCl[b]	181-186	50	$C_{21}H_{22}ClNOS$
42	CH_2CH_3	Cl	CH_3	$N(CH_3)_2$	HCl[b]	134-137	55	$C_{22}H_{24}ClNOS$
43	$CH(CH_3)_2$	H	H	$N(CH_3)_2$	oxalate[b]	88-90	25	$C_{22}H_{25}NOS$
44	$CH(CH_3)_2$	H	CH_3	$N(CH_3)_2$	oxalate[b]	165-171	25	$C_{23}H_{27}NOS$
45	$(CH_2)_2CH_3$	H	H	$N(CH_3)_2$	HCl	199-204	14	$C_{23}H_{25}NOS$
46	$(CH_2)_2CH_3$	H	CH_3	$N(CH_3)_2$	HCl[b]	121-125	30	$C_{23}H_{27}NOS$
47	$(CH_2)_3CH_3$	H	H	$N(CH_3)_2$	HCl	192-195	40	$C_{23}H_{27}NOS$
48	$(CH_2)_3CH_3$	H	CH_3	$N(CH_3)_2$	HCl[b]	183-185	37	$C_{24}H_{29}NOS$
49	CH_2CH_3	H			HCl[b]	240-243	55	$C_{22}H_{23}NOS$

[a] All compounds were analyzed for C, H, N, and Cl, and the results were within 0.4% theory. [b] Anal. calcd for 0.5 mol of H_2O. [c] Single isomer. See Experimental Section. [d] *Z* isomer. See ^1H NMR in Experimental Section. [e] Anal. calcd for 0.25 mol of H_2O. [f] 2:1 mixture of *Z* and *E* isomers. See ^1H NMR in Experimental Section. [g] Anal. calcd for 1 mol of H_2O. [h] Anal. calcd for 1.5 mol of H_2O.

7-chloro compound (**4**). The 2-acyl-7-chlorothioxanthene derivatives (**32**, **33**, **41**, and **42**) were potent in the cat test, but in this series the maximum ratio of activity in the decerebrate cat to activity in the mouse test was obtained with the 2-propionyl-8-chloro compound (**41**), and not the acetyl compound as was found in the phenothiazine series.

Compounds **39** and **40**, where the dimethylamino group was replaced by a piperazinyl and morpholino group, respectively, were active in the cat test but were moderately sedative. The piperidylidene derivative (**49**) was potent in reducing decerebrate rigidity but was again sedative. This is of interest, as this type of structure is not normally associated with high neuroleptic potency but is normally found in antihistaminics and antiemetic tricyclic compounds.[12]

The two isomers of the disubstituted compound, **32** and **33**, showed similar activity in both the cat and the mouse test. The propionyl derivative (**35**, *Z* isomer) was less potent in reducing decerebrate rigidity than the isomeric mixture (**36**, 2:1 mixture of *Z* and *E* isomers, respectively) but was less sedative. It is of interest that the *Z* isomer of chlorprothixene is a considerably more potent psychotherapeutic agent than is the *E* isomer.[13] Thus, a selectivity of action in reducing decerebrate rigidity over sedative and other effects may be achieved by an investigation of the *E* isomers of this type of compound.

A number of compounds which were potent in reducing decerebrate rigidity and had a relative lack of potency in the motor activity test were further examined for their oral activity in the decerebrate cat. The 2-chloro-8-acyl derivatives (**32**, **33**, **41**, and **42**) were inactive orally in the cat, as was the branched-chain aminopropylidene compound (**34**). The straight-chain aminopropylidene derivatives (**30**, **35**, and **36**) had good oral activity in the cat with a satisfactory duration of action (greater than 3 h). The saturated thioxanthene compounds (**51**, **52**, and **53**) showed some activity intravenously in the cat but were inactive when dosed orally. The carbinols (**50** and **54**) were inactive.

The structures of the most potent acyl-substituted thioxanthenes in reducing decerebrate rigidity in the cat contain the structural features found most commonly in the more potent tricyclic psychotherapeutic agents. The many and diverse actions of such agents in the CNS probably involve the modulation of more than one neurotransmitter. Thus, modification of the structure of the thioxanthene psychotherapeutic agent chlorprothixene has led to the separation to some extent of the activity in reducing decerebrate rigidity from that of sedative effects. This may reflect a selectivity of action involving noradrenaline receptors rather than dopamine receptors.

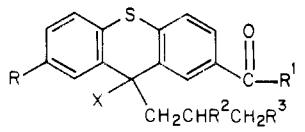
Experimental Section

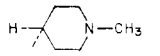
Biological Methods. Reduction of Intercollicular Decerebrate Rigidity in the Cat. (1) **Intravenous.** The method described by Maxwell[18] was used. Briefly, under halothane anesthesia, the midbrain was sectioned between the colliculi. The anesthesia was discontinued and at least 1 h elapsed before recording the integrated electromyographic response of the quadriceps muscle to controlled stretches. The drug under test was infused intravenously in a saline solution in graded doses and the stretch response repeated. The dose of the compound which reduced the stretch response by 50% was determined.

(2) **Oral.** The compound in a gelatine capsule was administered orally to conscious cats. One hour later, the animal was decer-

(12) E. Usdin and D. H. Efron in "Psychotropic Drugs and Related Compounds", 2nd ed, DHEW Publication No. (HSM) 72-9074.
(13) J. Dunitz, H. Esv, and P. Strickler, *Helv. Chim. Acta*, 47, 1897 (1964).

Table V. Compounds 50-54



no.	R	R^1	R^2	R^3	X	salt	mp, °C	yield, %	formula[a]
50	H	CH_3	CH_3	$N(CH_3)_2$	OH	oxalate[b]	71-75	25	$C_{21}H_{25}NO_6S$
51	H	CH_3	CH_3	$N(CH_3)_2$	H	HCl[c]	209-211	15	$C_{21}H_{25}NOS$
52	H	CH_3	H	$N(CH_3)_2$	H	HCl[d]	173-177	25	$C_{20}H_{23}NOS$
53	Cl	CH_2CH_3	H	$N(CH_3)_2$	H	HCl[b]	241-243	15	$C_{21}H_{24}ClNOS$
54	H	CH_2CH_3			OH	HCl[c]	224-226	20	$C_{22}H_{25}NO_2S$

[a] All compounds were analyzed for C, H, and N, and the results were within 0.4% of theory. [b] Anal. calcd for 1.5 mol of H_2O. [c] Anal. calcd for 0.5 mol of H_2O. [d] Anal. calcd for 0.25 mol of H_2O.

Table VI. Pharmacological Activity of Acylthioxanthenes

no.	act. A[a] iv	act. B[b] po	motor act.[c]	ratio of motor act./ act. A
29	1.31		94	72
30	0.54	<5.4 (2)	33	60
31	1.19		192	161
32	0.81	>5.4 (2)	96	119
33	0.53	>5.4 (2)	89	168
34	0.52	>5.2	261	501
35	0.45	1.9	339	753
36	0.15	1.8	120	800
37	4.14		280	68
38	6.50		>659	>101
39	0.67		42	43
40	0.27		125	463
41	1.08	>9.6	695	644
42	1.30	>9.3	534	411
43	0.40		89	218
44	0.67		145	216
45	1.50	5.0-12.5	>501	334
46	1.22		195	160
47	1.35			
48	3.29		132	40
49	0.68		96	141
50	3.17 (1), >21.18 (1)			
51	2.08	>13.0 (2)	377	181
52	0.90	5.5-13.7	57	63
53	6.17		343	56
54	19.39		>485	>25
1	0.25	2.0	39	156
2	4.67	8.1	860	184
3	0.65	1.2	136	209
4	0.32	1.0	161	506
5	4.01	>6.1	103	26
6	0.39	2.1	11	28
7	0.03	1.0	11	393

[a] Dose, in μmol/kg iv, to reduce the integrated electromyographic response by 50%. [b] Dose, in μmol/kg po, to reduce the rigidity rating to 50% of the control. [c] Dose, in μmol/kg po, to reduce the locomotor activity count to 50% of the control.

ebrated and rated at 10-min intervals for 60–90 min for rigidity to all limbs. The dose of the compound required to reduce the score in the period 30–60 min after decerebration to 50% of that in the untreated control animals was determined.

Reduction of Locomotor Activity in the Mouse. The method described by Dews was used,[14] modified by administering the drug by the oral route and 1 h later measuring the locomotor activity for 5 min.

(14) P. B. Dews, *Br. J. Pharmacol. Chemother.*, 8, 46 (1953).

Synthesis. Melting points were determined on an "Electrothermal" instrument. Novel and fully characterized intermediates are listed in Tables I–III.

Preparation of Tricyclic Ketones (Table II). A mixture of the 2-[(4-acylphenyl)thio]benzoic acid (prepared by the general method of Raseanu[8]) and ten times its weight of PPA was heated with stirring at 60–70 °C for 4 h and was then poured onto ice. The solid was collected, washed (2 N NaOH), and recrystallized. Alternatively, the ketone was extracted with $CHCl_3$, the extract was washed (2 N $NaHCO_3$ solution) and dried ($MgSO_4$), and the solvent was removed to give a solid which, on recrystallization, yielded the ketone.

Preparation of Ketal Derivatives (Table III). The preparation of **22** is an example of this procedure. The tricyclic ketone **15** (20 g, 0.08 mol) and ethylene glycol (27.7 g, 25 mL, 0.48 mol) in dry toluene (750 mL), containing *p*-toluenesulfonic acid (0.075 g), were stirred at reflux for 16 h, water being separated in the usual manner. After cooling, the solution was stirred with anhydrous potassium carbonate (7 g) and filtered. The solvent was removed in vacuo to give a solid which, on recrystallization, gave the ketal **22**.

Preparation of Thioxanthenes (Table IV). Ethyl bromide (0.1 mL) was added to Mg turnings (0.89 g, 0.04 g-atom) in dry THF (50 mL), containing a crystal of iodine. After reaction was initiated, the appropriate chloroalkylamine (0.04 mol) [3-(dimethylamino)propyl chloride,[15] 3-(dimethylamino)-2-methylpropyl chloride,[16] 3-(dimethylamino)-2-ethylpropyl chloride,[17] 3-*N*-morpholino-2-methylpropyl chloride,[18] 3-(4-methylpiperazin-1-yl)propyl chloride,[19] 3-*N*-morpholinopropyl chloride,[20] or 4-chloro-1-methylpiperidine] in dry THF (10 mL) was added at a rate to maintain reflux. The mixture was stirred and refluxed for 2 h and cooled (0 °C), and the ketal (0.02 mol) in dry THF (15 mL) was added with stirring during 20 min. The mixture was then stirred and refluxed for 4 h and was cooled (0 °C), and aqueous NH_4Cl (saturated solution) was added slowly. The organic layer was separated and dried ($MgSO_4$), and the solvent was removed in vacuo to give the crude carbinol. The tricyclic carbinol (0.02 mol) in glacial acetic acid (50 mL), containing H_2SO_4 (2 N, 70 mL), was refluxed for 2 h. The cooled solution was made alkaline with ammonia and the mixture extracted with ether. Evaporation of the extract in vacuo gave an oil, which was chromatographed on silica gel. Elution with chloroform gave an oil, which was dissolved in dry ether and treated with the appropriate acid to give the olefin, as its salt.

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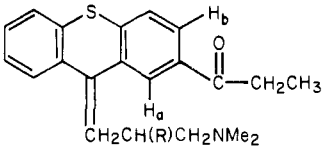
Table VII. Chemical Shifts (δ, ppm) and ΔEu values (ppm) for compounds in $CDCl_3$/internal standard Me_4Si (1%)



no.	sample wt, mol	H_a	H_b	$COCH_2CH_3$	NMe_2	H_c	stereochem assignment
34	1.48×10^{-5}	8.03 (d) [-3.8][a]	7.70 (q) [-2.3]	3.02 (q) [-2.4]	2.11 (s) [-10.0]	5.65 (d) [-3.5]	1:1 *Z* & *E*
		8.15 (d) [-6.5]	7.85 (q) [-2.3]	3.02 (q) [-2.7]	2.14 (s) [-10.0]	5.77 (d) [-5.2]	isomeric mix.
36	1.6×10^{-5}	8.03 (d) [-5.3]	7.75 (q) [-1.5]	2.97 (q) [-2.2]	2.20 (s) [-8.1]	5.95 (t) [-3.7]	2:1 *Z* & *E* isomeric mix.
35	1.59×10^{-5}	8.03 (d) [-5.3]	7.75 (q) [-1.5]	2.98 (q) [-2.2]	2.30 (s) [-8.2]	5.97 (t) [-3.9]	*Z* isomer

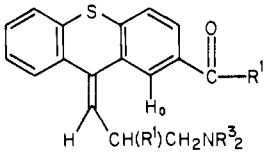
[a] ΔEu values are in brackets.

Catalytic Hydrogenation of Olefins (Table V). This method is exemplified by the hydrogenation of **30**. The olefin **30**, as its free base (3.8 g), in ethanol (150 mL) was hydrogenated at 25 °C at an initial pressure of 300 psi, over 5% Pd/C catalyst (0.3 g). After the uptake was complete (24 h), the mixture was filtered and the solvent removed in vacuo. The residual oil was dissolved in dry ether and treated with ethereal HCl to give the thioxanthene **52** as the hydrochloride.

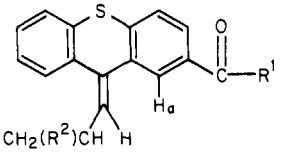
Isolation of the Carbinols (Table V). The preparation of **50** is an example of this procedure. The carbinol (7.0 g) was refluxed in methanol (100 mL), containing *p*-toluenesulfonic acid (0.2 g), for 2 h. Evaporation of the solvent in vacuo gave a brown gum (6.2 g), which was dissolved in ether, and the solution was extracted with acetic acid (2 N). The acid extract was made alkaline with NaOH solution and the mixture extracted with ether. The ether extract wad dried and on evaporation gave an oil (1.4 g). The oil was chromatographed on silica gel, using chloroform as eluent, to give the carbinol **50**, which was isolated as the oxalate salt (1.0 g) in the usual manner.

Separation of the Geometrical Isomers. The separation of the isomers **32** and **33** is an example of this procedure. The isomeric mixture (as the HCl salts) was fractionally crystallized from alcohol, isomer **32** being the less-soluble isomer.

^{1}H NMR Determinations. ^{1}H NMR spectra[21] of the thioxanthenes (Table IV) were initially determined at 30 °C using a Varian A60D spectrometer. This demonstrated, in the majority of cases, the presence of approximately equal mixtures of the *Z* and *E* isomers. (H_a in the *Z* isomer showed as a doublet downfield



Z isomer



E isomer

from the H_a doublet of the *E* isomer.) This was confirmed for certain compounds using an europium-shift reagent as follows.

Solutions were prepared by adding approximately 5 mg of the test compound (as the free base) to 0.5 mL of $CDCl_3$. ^{1}H NMR spectra were obtained at 30 °C using a Varian CAT 20 spectrometer. Tris(dipivalomethanato)europium [$Eu(DPM)_3$] was then added to the solution, and the spectra were recorded again. The ΔEu value[22] for each relevant proton was derived from the slope of the straight line obtained by plotting the magnitude of the shift induced at various values of the molar ratio of $Eu(DPM)_3$ to solute (see Table VII).

Acknowledgment. The authors thank Dr. M. L. Podmore for the spectral measurements and Mrs. A. Kalsi, B. Doggett, and J. Patrick for technical assistance.

(21) Solutions were prepared by adding approximately 50 mg of the test compound (as its free base) to 0.5 mL of $CDCl_3$.

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Alkylating Nucleosides. 4. Synthesis and Cytostatic Activity of Chloro- and Iodomethylpyrazole Nucleosides

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The synthesis and cytostatic activity of several chloromethyl- and iodomethylpyrazole nucleosides are described. Glycosylation of ethyl 3(5)-(chloromethyl)pyrazole-5(3)-carboxylate (**3**) and 3(5)-(chloromethyl)pyrazole-5(3)-carboxamide (**4**) with poly(O-acetylated) sugars via an acid-catalyzed fusion method gave the corresponding 3-(chloromethyl)-5-carboxylate and 3-(chloromethyl)-5-carboxamide substituted nucleosides **7** and **9**, respectively. From the reaction of **4** with tetra-*O*-acetyl-β-D-ribofuranose, the 5-(chloromethyl)-3-carboxamide-substituted derivative **11** was also obtained. Reaction of **7**, **9**, and **11** with sodium iodide in acetone provided the related iodomethylpyrazole nucleosides **8**, **10**, and **12**. In general, chloromethyl-substituted nucleosides showed moderate activities against HeLa cells, while all the corresponding iodomethyl derivatives exhibited high activities. Some of these latter compounds increased the life span of mice bearing ECA tumor.

In previous papers of this series,[1-4] we have reported the synthesis, cytostatic activity, and mode of action of several halomethyl-1,2,3-triazole and bromomethylpyrazole nucleosides **1** and **2**, as a new type of alkylating agents. The

0022-2623/80/1823-0657$01.00/0