equilibrated for 1 h with a solution change every 15 min. Two successive control contractions were elicited at 15-min intervals with 5×10^{-7} M *cis*-2-methyl-4-[(dimethylamino)methyl]-1,3-dioxolane methiodide (CD). The isometric contractions were recorded with a force displacement transducer (FT 03.D) on a Grass physiograph. The mean of the two contractile responses was taken as the 100% value for the tonic (slow) component of the response. The muscle was washed with Hepes saline solution and was allowed to reequilibrate. The calcium antagonist was added 10 min before the dose–response for CD was determined. The drug-induced inhibition of contraction was expressed as percent of control. The ID_{50} values were graphically determined from the concentration–response curves. The pharmacological test results are summarized in Table I.

Competitive [^{3}H]Nitrendipine Binding Assay.[21] The inhibition of [^{3}H]nitrendipine binding to a microsomal fraction from guinea pig ileal longitudinal smooth muscle was carried out by using the procedure reported by Bolger et al.[21]

Acknowledgment. We are grateful to the Medical Research Council of Canada (Grant MT-8892) for financial support of this work and to the Alberta Heritage Foundation for Medical Research for Studentships (to L.D. and M.C.L.K.K.).

Registry No. **2** ($R_1 = R_2 = CO_2Me$), 73349-75-4; **2** ($R_1 = R_2 = CO_2Et$), 23125-30-6; **2** ($R_1 = R_2 = CO_2$-*i*-Pr), 104196-54-5; **2** ($R_1 = R_2 = CO_2$-*i*-Bu), 104196-55-6; **2** ($R_1 = CO_2$-*i*-Bu, $R_2 = CO_2Me$), 104196-46-5; **2** ($R_1 = CO_2$-*i*-Pr, $R_2 = CO_2Me$), 39562-56-6; **2** ($R_1 = CO_2Me$, $R_2 = CN$), 67593-36-6; **2** ($R_1 = CN$, $R_2 = CN$), 64089-24-3; **5** ($R_1 = R_2 = CO_2Me$), 23125-31-7; **5** ($R_1 = R_2 = CO_2Et$), 21197-70-6; **5** ($R_1 = R_2 = CO2$-*i*-Pr), 104196-57-8; **5** ($R_1 = R_2 = CO_2$-*i*-Bu), 104196-58-9; **5** ($R_1 = CO_2Me$, $R_2 = CO_2$-*i*-Bu), 104196-49-8; **5** ($R_1 = CO_2$-*i*-Pr, $R_2 = CO_2Me$), 104196-48-7; **5** ($R_1 = R_2 = CN$), 64089-25-4; **7a**, 106457-24-3; **7b**, 106457-25-4; **8a**, 106457-26-5; **8b**, 106457-27-6; **9a**, 106457-28-7; **9b**, 106457-29-8; **10a**, 106457-30-1; **10b**, 106457-31-2; **11a**, 106457-32-3; **11b**, 106457-33-4; **12a**, 106457-34-5; **12b**, 106457-35-6; **13a**, 106457-36-7; **13b**, 106457-37-8; **14a**, 106457-38-9; **14b**, 106457-39-0; **15a**, 106457-40-3; **15b**, 106457-41-4; **16a**, 106457-42-5; **16b**, 106457-43-6; **17a**, 106457-44-7; **17b**, 106457-45-8; **18a**, 106457-46-9; **18b**, 106457-47-0; **19a**, 106457-48-1; **19b**, 106457-49-2; **20a**, 106457-50-5; **20b**, 106457-51-6; **21a**, 106457-52-7; **21b**, 106457-53-8; **22a**, 106457-54-9; **22b**, 106457-55-0; **23a**, 106457-56-1; **23b**, 106457-57-2; **24a**, 106469-33-4; **24b**, 106457-58-3; **25a**, 106457-59-4; **25b**, 106457-60-7; **26a**, 106457-61-8; **26b**, 106457-62-9; **27a**, 106457-63-0; **27b**, 106457-64-1; **28a**, 106457-65-2; **28b**, 106457-66-3; **29a**, 106457-67-4; **29b**, 106457-68-5; **30**, 106457-69-6; **31**, 106457-70-9; **32**, 106457-71-0; **33**, 106457-72-1; **34**, 106457-73-2; **35**, 106457-74-3; **36**, 106457-75-4; **37**, 106457-76-5; **38**, 106469-34-5; **39**, 106457-77-6; **40**, 106457-78-7; **41**, 106457-79-8; **42**, 106469-35-6; **43**, 106457-80-1; $ClCO_2Me$, 79-22-1; $ClCo_2Bu$-*t*, 24608-52-4; $ClCO_2Ph$, 1885-14-9.

Steroidal Silicon Side-Chain Analogues as Potential Antifertility Agents

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A number of silicon-substituted analogues of ethynylestradiol that exhibit modified and enhanced biological activities have been synthesized. Particularly noteworthy are a group of [(trialkylsilyl)ethynyl]estradiol analogues that exhibit high antifertility potency and markedly reduced estrogenic activity. The best compounds synthesized are 17α-[(triethylsilyl)ethynyl]estradiol (**5**) and 17α-[(*tert*-butyldimethylsilyl)ethynyl]estradiol (**33**), which show a separation of antifertility from estrogenic activity in the rat. The results of structure–activity studies indicate a good correlation between the observed biological activities and the calculated van der Waals volumes of the three variable silicon substituents.

Oral contraceptives, because of their long-term benefit-to-risk ratio, have been considered a major scientific advance in family planning since their introduction in 1960. However, the adverse side effects associated with the estrogenic components (ethynylestradiol or mestranol) of the "pill" have led to persistent anxieties among regulatory agencies, doctors, and users.[1] Estrogens have been implicated in breast cancer, endometrial carcinoma, and thromboembolic diseases.[2] Because of these concerns, the development of new estrogens as potential antifertility agents should focus on obtaining antifertility activity accompanied by a greatly diminished estrogenic activity.

Previous studies[3] have indicated that silicon-containing compounds used as medicinal agents can retain and/or improve their biological profile in comparison with that of their corresponding carbon isostere. For example, toxicity of the silacarbamate analogues of meprobamate was less than that of their carbon analogues at equipotent biological activities.[4] Furthermore, the trimethylsilyl ether of testosterone, Silandrone, has been described as a clin-

Scheme I

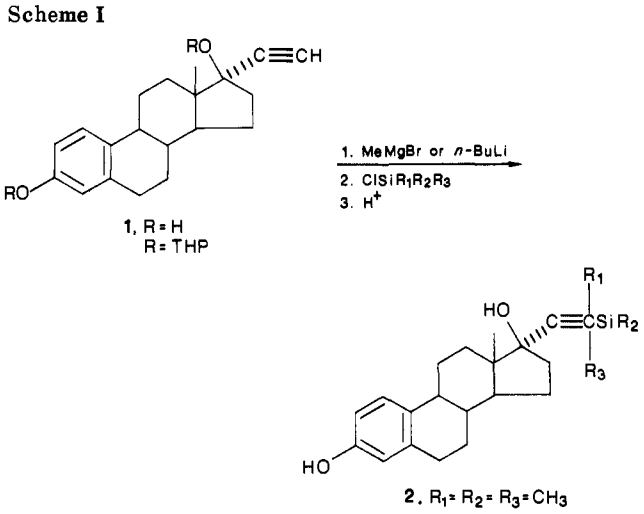

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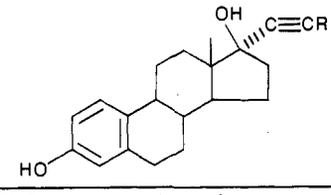
Table I. Oral Antifertility and Oral Estrogenic (Uterotropic) Potencies of Silyl-Substituted EE Analogues Relative to EE in Rats



no.	R	antifertility[c] potency: *A*	estrogenic potency: *E*	separation: *A*/*E*	purifn[d]	mp, °C	meth[e]	yield,[f] %
1	H	100	100[a]					
2	$SiMe_3$	33[a]	7.0[a]	4.7	U, X	174–175	A	62
3	$SiMe_3$, 3-methyl ether	33[a]	8.0[a]	4	X	83–87	A	92
4	CMe_3	1[a]	0.07[a]	14	X	124–126		27
5	$SiEt_3$	600	37	16	W	170–172	A	81
6	CEt_3	0 @ 3.2 mg/kg per day	0 @ 1000 μg		U, V	145–147		41
7	Si(*n*-Pr)$_3$	200[a]	25[a]	8	U, X	96–98	A	67
8	Si(*n*-Bu)$_3$	0 @ 3 mg/kg per day[a]	2.5[a]		U	gum	A	55
9	Si(*n*-Bu)$_3$, 3-acetate	0 @ 3 mg/kg per day	4.0[a]		X	84–86		80
10	$Si(Me_2)CH_2CH{=}CH_2$	250[a]	24[a]	10	U, X	151–153	A	55
11	$Si(Me_2)CH_2Br$	200[a]	27[a]	7.4	U, X	183–185	A	52
12	$Si(Me_2)CH_2Ph$	300	12	25	U, W	142–145	B	42
13	Si(Et$_2$)-*n*-C_6H_{13}	15	5.2	3	U	gum	B	47
14	Si(Et$_2$)-*t*-Bu	300	31	10	U, V	167–168	C	73
15	Si(Et$_2$)-*n*-Pr	300	39	8	U, V	127–128	B	44
16	Si(Me$_2$)-*n*-Pr	300	22	14	U, X	156–158	B	72
17	Si(Et$_2$)-*i*-Pr	300	30	10	U, V	144–146	C	56
18	Si(Me$_2$)-*i*-Pr	300	15	20	U, V	150–152	C	63
19	Si(Me$_2$)-*n*-Bu	300	20	15	U, Y	121–122	C	71
20	$Si(Me)(Et)CH{=}CH_2$	300	28	11	U, Z	182–184	C	28
21	Si(Et$_2$)OH	300[b]	11[b]	27		gum		19
22	$Si(Me)(CH_2Cl)_2$	150	39	4	U, W	194–195	B	27
23	$Si(Me_2)CHCl_2$	300	18	17	U, W	191–192	B	21
24	$Si(Me_2)CHClCH_3$	300	45	7	U, W	175–176	C	61
25	$Si(Me_2)(CH_2)_2CH_2Cl$	200	25	8	U, V	130–132	C	57
26	$Si(Me_2)(CH_2)_2CF_3$	150	19	8	U, W	137–138	C	63
27	$Si(Me_2)CH_2Cl$	150	17	9	U, W	179–181	A	71
28	Si(Me$_2$)Ph	33[a]	7[a]	4.7	W	122–126	A	43
29	$SiPh_3$	0 @ 1.0 mg/kg per day	0.5		U, X	123–125	A	77
30		250[a]	25[a]	10	V	174–175	A	71
31		200,[a] 200	85,[a] 10 20 40	2.4, 20 10 5	U, V	182–183	A	67
32		500[a]	120[a]	4.2	U, X	189–192	A	65
33	Si(Me$_2$)-*t*-Bu	600	20	30	W, V	179–181	A	73
34	Si(Et$_2$)Me	600	40	15	U, V	180–182	B	70
35	Si(Et$_2$)Ph	150	17	10	U, X	129–130	B	71
36	Si(Et$_2$)H	600	29	21	U, W	161–163	B	20
37	$Si(Et_2)CH_2CH{=}CH_2$	300	44	7	U, X	148–149	B	30
38	$(EE)_2SiEt_2$ dimer	0 @ 128 μg	8		V	122–125		31
39	Si(Et$_2$)-*sec*-Bu	300	57	5	U, X	121–123	C	52
40	Si(Me$_2$)-*sec*-Bu	300	20	15	U, X	144–146	C	46
41	$Si(Me_2)(CH_2)_2C{\equiv}N$	300	37	8	U, W	154–155	C	32
42	$Si(Et_2)C{\equiv}CH$	600	37	16	U	gum		2

[a,b] Testing was performed at Mason Labs unless otherwise noted as *a* for Endocrine Labs or *b* for SRI's testing program. [c] Minimum protective doses for prevention of pregnancy: 200 μg, Mason Labs; 100 μg, Endocrine Labs and SRI. [d] Purification: U, dry column chromatography using $CHCl_3$/5% EtOAc; V, recrystallization, methanol; W, recrystallization, methylene chloride; X, recrystallization, ether/hexane; Y, recrystallization, benzene; Z, recrystallization, acetone/pet ether. [e] Methods A, B, and C, including reaction conditions, are described in the Experimental Section. [f] Yields were not optimized.

ically useful, long-lasting androgen.[5] We sought to incorporate silicon in the design of steroidal antifertility agents to investigate the possible beneficial features.

It is well-known that replacement of the acetylenic hydrogen of 17α-ethynyl steroids by halogen, methyl, or another ethynyl group leads to enhanced antifertility activity.[6] To evaluate whether the substitution of silicon has a potentially useful role in endocrine activity, we introduced a silicon atom onto the ethynyl group of ethynylestradiol (EE) (Scheme I) or hydrosilylated the triple bond to give the regioisomeric vinylsilanes (Scheme II). These modified steroids displayed antifertility activity with the desired separation of unwanted estrogenic activity (Table I).

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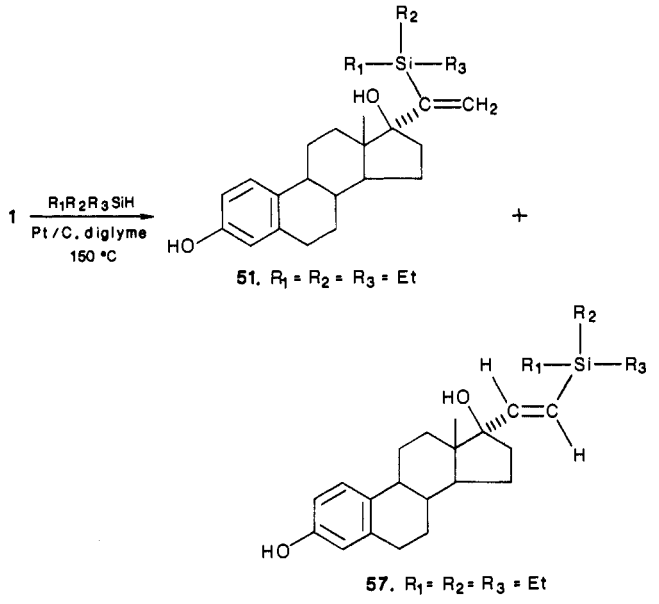
Chemistry

The alkyl-, aryl-, alkynyl-, and alkenylsilyl-substituted 17α-2′-ethynylestradiol derivatives **2–42** were generally available from the reaction of 17α-acetylide anions with

Scheme II

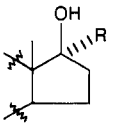


various silyl chlorides (Scheme I). The acetylides were generated upon treatment of EE with methylmagnesium bromide[7] (method A) or *n*-butyllithium (method B).[8] For example, EE (1) was reacted sequentially with excess methylmagnesium bromide in tetrahydrofuran and excess trimethylchlorosilane, whereupon 17α-[(2-trimethylsilyl)-ethynyl]estradiol 3,17-bis(trimethylsilyl ether) was formed. The silyl ethers were cleaved by subsequent mild acid-catalyzed methanolysis to yield (trimethylsilyl)alkyne **2**, which was purified by chromatography on silica gel followed by crystallization. Various silicon substituents from alkyl through aryl were also examined. The requisite chlorosilanes were available from commercial sources or were readily prepared from the reaction of silicon tetrachloride with the appropriate Grignard reagents at different stoichiometric ratios. Attempts to synthesize other, more complex silicon analogues such as **10**, **23–25**, and **37** via addition of dialkyldichlorosilane to the steroid acetylide derivative followed by treatment with an appropriate lithium alkyl reagent resulted only in bis-2-(17α-ethynylestradiol)dialkylsilane dimer formation. However, the desired analogues were obtained when the mixed trialkylchlorosilanes were generated from the dialkyldichlorosilanes in situ before reaction with the steroid acetylide.

For comparison, the carbon isostere analogues **4** and **6** were prepared by respective addition of (3,3-dimethylbutynyl)magnesium bromide[9] and (3,3-diethylpentynyl)-magnesium bromide[9] to estrone.

The silylvinyl analogues of EE were available by either of two methods: (1) Production of *cis*-17α-(2-vinyl)silanes **50** and **53** was achieved upon partial hydrogenation of the corresponding 17α-[(trialkylsilyl)ethynyl]estradiol derivatives with palladium on barium sulfate.[10] (2) The *trans*-17α-[2-(trialkylsilyl)vinyl] analogues (**50**, **52**, **55**, **57**, and **59**) and the internal adduct 17α-[1-(trialkylsilyl)vinyl] derivatives (**48**, **51**, **54**, and **56**) were prepared by the general route shown in Scheme II. In this procedure,[11] 5% platinum on carbon in diglyme at 150 °C catalyzed the addition of trialkylsilanes to the ethynyl group of 17α-ethynylestradiol, affording a 1:1 regioisomeric mixture of olefins, which were separated by chromatography. The straightforward stereochemical assignments of the silylvinyl analogues (**48–59**) were possible upon comparison with known vicinal and geminal proton coupling constants and chemical shift data,[12] as shown in Table II.

Table II. NMR Data of Vinylsilane Analogues[a]



no.	R	shift: δ, ppm	$J_{H_AH_B}$, Hz
48[b]	$(SiMe_3)C=CH_{2AB}$	H_{AB}, 5.42 (d); 5.56 (d)	1.3
49[b]	$CH_A=CH_BSiMe_3$ (*E*)	H_A, 6.22 (d); H_B, 5.77 (d)	19
50	$CH_A=CH_BSiMe_3$ (*Z*)	H_A, 6.57 (d); H_B, 5.51 (d)	14
51[c]	$(SiEt_3)C=CH_{2AB}$	H_{AB}, 5.52 (d); 5.57 (d)	1.0
52[c]	$CH_A=CH_BSiEt_3$ (*E*)	H_A, 6.34 (d); H_B, 5.66 (d)	19
53	$CH_A=CH_BSiEt_3$ (*Z*)	H_A, 6.70 (d); H_B, 5.42 (d)	14
54	$[Si\text{-}(n\text{-}Pr)_3]C=CH_{2AB}$	H_{AB}, 5.52 (d); 5.56 (d)	1.0
55	$CH_A=CH_BSi\text{-}(n\text{-}Pr)_3$ (*Z*)	H_A, 6.34 (d); H_B, 5.67 (d)	19
56	$[Si\text{-}(n\text{-}Bu)_3]C=CH_{2AB}$	H_{AB}, 5.50 (d); 5.53 (d)	1.0
57	$CH_A=CH_BSi\text{-}(n\text{-}Bu)_3$ (*Z*)	H_A, 6.26 (d); H_B, 5.70 (d)	19
58[b]	$(SiPh_3)C=CH_{2AB}$	H_{AB}, 5.86 (d); 5.74 (d)	1.1
59[b]	$CH_A=CH_BSiPh_3$ (*E*)	H_{AB}, 6.32 (d); 6.38 (d)	19

[a] Spectra were obtained by using a Varian A-60A or XL-100 with $CDCl_3$ as the solvent unless othersise noted. [b] Spectra were obtained by using a Varian XL-400 with CD_3Cl_3 as the solvent. [c] Solvent consisted of $CDCl_3$ + 0.1 mL of CD_3OD.

Biology

With the substituted silylethynyl and silylvinyl derivatives of estradiol in hand, we sought to establish which combination of groups on silicon provides the most potent antifertility activity with minimal estrogen activity. The most biologically promising compounds that resulted from these studies, as shown in Table I, were the triethylsilyl analogue **5** and the *tert*-butyldimethylsilyl analogue **33**. In rats, **5** and **33** were 6 times more potent than EE as oral antifertility agents but were only 37% and 20%, respectively, as potent as oral estrogens. To demonstrate that silicon is essential in altering these biological activities, we synthesized and compared the carbon isosteres **4** and **6** of the trimethylsilane **2** and the triethylsilane **5**. In rats, **4** and **6** were essentially devoid of antifertility activity at 3.2 mg/kg per day and of oral estrogenic activity at a total dose of 1000 μg. These findings firmly established that the presence of a trialkylsilyl group on the ethynyl group of EE profoundly altered and enhanced biological activity.

Initially, the two most potent compounds with the largest separation of estrogenic and antifertility activity were the *tert*-butyldimethylsilyl analogue **33** and the triethylsilyl analogue **5**. We therefore examined several analogues where two of the alkyl groups were kept as either methyl or ethyl and the third group was varied as represented by R_1.

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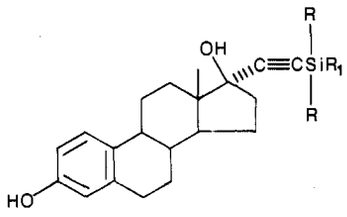
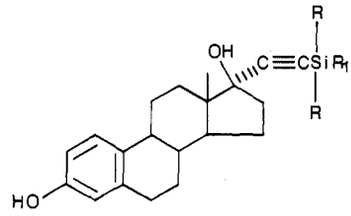


R = Me or Et R_1 = H, OH, *n*-Pr, *i*-Pr, *n*-Bu, *s*-Bu, *t*-Bu, vinyl, allyl, benzyl, ethynyl

Introduction of an allyl substituent to the dimethylsilyl moiety, as in compound **10**, produced potent oral antifertility activity and reduced oral estrogenic activity relative to the trimethyl analogue **3**, resulting in a 10-fold separation of activities relative to EE. The corresponding compound in the diethyl series, **37**, is 3 times as active as EE in the antifertility screen and has 44% of the estrogenic activity, with a 7-fold separation. The substitution of ethyl for methyl in this case resulted in small increases in antifertility potency and estrogenic activity. The dimethylbenzylsilane **12** was 3 times as active as EE in the antifertility assay, with a 25-fold separation from estrogenic activity. The large separation ratio of the benzyl-substituted analogue **12** suggests that further modifications of this group may have even greater antifertility potency and lower estrogenic potency. In summary, most of these analogues were not as active as the triethylsilane **5** or dimethyl-*tert*-butylsilane **33** as antifertility agents, nor did they show any significant reduction of estrogenicity. In overall comparison of the dimethyl and diethyl series of silane compounds listed in Table I, the dimethyl series was superior to the diethyl series in reducing estrogenic activity.

Interestingly, it was found that the diethylsilane derivative **36** (R = Et, R_1 = H) was as active as the triethylsilane analogue **5** as an antifertility agent and showed an additional 20% reduction in estrogenicity. We speculated that this silane derivative (**36**) could be readily metabolized to



21, R = Et, R_1 = OH
36, R = Et, R_1 = H

give the silanol **21**.[13] Similarly, the silanol analogue **21** could be a likely metabolite of the triethyl analogue **5** via enzymatic hydroxylation at the carbon β to silicon on one of the ethyl groups followed by elimination.[14] To test our hypothesis, compound **21** was synthesized, and biological assays showed that the silanol was indeed equivalent to the triethylsilane **5** as an antifertility agent and was only one-third as estrogenic.

Initial attempts to define structure–activity relationships with Hansch-type solvent partition coefficients within the trisubstituted-silicon analogues yielded no useful correlation, nor did cursory examination of silicon-substituent interactions with either Drieding models or CPK space-filling models. The qualitative relative rates of sodium methoxide cleavage[13] of the [(trialkylsilyl)ethynyl]estradiol derivatives also failed to show a correlation with biological activity. However, calculation and summation of the van der Waals volumes for the three variable alkyl substituents on silicon with use of published values[15] for substituent volumes revealed a useful correlation between biological activity and molecular volume. The calculated van der Waals volumes (Vw, cm^3/mol) are shown in Table III, and the pertinent biological data are presented in Table I.

From the number of examples available in Table I, definite trends between van der Waals volume and biological activity could be discerned. Analogues with the three groups on silicon with Vw larger than 105 cm^3/mol and smaller than 50 cm^3/mol were immediately ruled out because they led to inactive compounds. Within this range, compounds with Vw between 51 and 72 cm^3/mol showed antifertility potency 6 times that of EE. The maximum desired biological effect was produced by incorporation of the two methyl groups with a combined $Vw_{R_1} + Vw_{R_2}$ of 27 cm^3/mol and a variable group with a Vw_{R_3} of 23–45 cm^3/mol. A Vw increase from dimethyl-R to diethyl-R resulted in an undesirable increase in estrogenic potency. This combination of substituents yielded improved compounds, as is best exemplified in the case of the *tert*-butyldimethylsilyl analogue **33**. This analogue had a Vw of 72, was only 20% as estrogenic as EE, and was 6 times as potent an antifertility agent as EE, affording the largest separation of estrogenic from antifertility activity observed to date. Perhaps improved antifertility agents may be obtained by holding the dimethyl substitution constant and varying the third substituent within the required Vw.

The van der Waals volume calculations of the silylethynyl analogues and correlation of these volumes with their experimental biological activities established a framework on which to base a systematic approach to synthesis of additional analogues. We chose to prepare compounds **22–27**, **41**, and **42**, each of which has an R_3 with a Vw that should provide the desired biological profile, according to our correlations. Indeed, these compounds were 1.5–6.0 times more active than EE as antifertility agents and 17–39% as estrogenic (Table I). The results show that the van der Waals volumes of the three variable silicon substituents are useful in determining the upper end limits for substitution on silicon to retain the antifertility potency while reducing the estrogenicity of these compounds.

In 1972, Wotiz and Scublinsky[16] reported that estriol 3-cyclopentyl ether was a potent oral antifertility agent with low estrogenic character. Curiously, the authors found that the contraceptive activity was particular to the 3-cyclopentyl ether derivative and was not the result of an enhanced solubility in tissue lipids. To determine whether we could observe a similar beneficial role, we decided to further derivatize previously prepared triethylsilane **5** to the esters **43–46** and the 3-cyclopentyl ether **47** (Table IV). Unfortunately, none of these derivatives showed any improvement over the parent analogue **5**, nor did they follow the expected trend in our structure–activity studies.

The vinylsilane series of compounds (**48–59**) exhibited weak oral estrogenic activity and modest antifertility activity (Table V). Compared with EE, the terminally substituted compounds had the largest separation of antifertility from estrogenic activity, with the cis compounds being the most potent. Comparison of the trimethyl compounds with the triethyl compounds indicates that variation of the alkyl group bound to silicon at the terminal end of the vinyl analogues has a pronounced effect on biological activity. The internally substituted vinylsilanes

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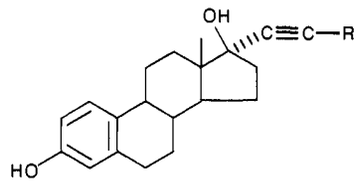
(15) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441.
(16) Wotiz, H. H.; Scublinsky, A. *Steroids* **1972**, *20*, 223.

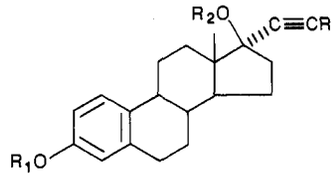
Table III. Calculation of van der Waals Volumes (Vw)[a] of Silicon Analogues of Ethynylestradiol

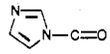


no.	R	Vw,[a] cm^3/mol	no.	R	Vw,[a] cm^3/mol
2	$SiMe_3$	41.0	**20**	$Si(Me)(Et)CH{=}CH_2$	58.0
5	$SiEt_3$	71.7	**21**	$Si(Et_2)OH$	55.8
7	$Si(n\text{-}Pr)_3$	103.4	**28**	$Si(Me_2)Ph$	73.2
8	$Si(n\text{-}Bu)_3$	133.1	**29**	$SiPh_3$	137.5
10	$Si(Me_2)CH_2CH{=}CH_2$	58.0	**33**	$Si(Me_2)$-*t*-Bu	71.5
11	$Si(Me_2)CH_2Br$	51.8	**34**	$Si(Et_2)Me$	61.5
12	$Si(Me_2)CH_2Ph$	83.4	**35**	$Si(Et_2)Ph$	93.6
14	$Si(Et_2)$-*t*-Bu	82.1	**36**	$Si(Et_2)H$	51.2
15	$Si(Et_2)$-*n*-Pr	61.5	**37**	$Si(Et_2)CH_2CH{=}CH_2$	78.4
17	$Si(Et_2)$-*i*-Pr	81.9	**39**	$Si(Et_2)$-*sec*-Bu	92.1
18	$Si(Me_2)$-*i*-Pr	61.5	**40**	$Si(Me_2)$-*sec*-Bu	71.7
19	$Si(Me_2)$-*n*-Bu	71.7			
	Analogues Chosen for Synthesis on the Basis of Their Calculated van der Waals Volumes				
22	$Si(Me)(CH_2Cl)_2$	58.6	**26**	$Si(Me_2)(CH_2)_2CF_3$	68.3
23	$Si(Me_2)CHCl_2$	58.6	**27**	$Si(Me_2)CH_2Cl$	58.6
24	$Si(Me_2)CHClCH_3$	60.0	**41**	$Si(Me_2)(CH_2)_2C{\equiv}N$	62.5
25	$Si(Me_2)(CH_2)_2CH_2Cl$	70.3	**42**	$Si(Et_2)C{\equiv}CH$	67.4

[a] Sum of van der Waals volumes of Si substituents $R_1 + R_2 + R_3$.

Table IV. Oral Antifertility and Oral Estrogenic (Uterotropic) Potencies of 3- and 17-Substituted Esters and Ethers of [(Triethylsilyl)ethynyl]estradiol Relative to EE in Rats



no.	R	R_1	R_2	antifertility potency: *A*	estrogenic potency: *E*
1	H	H	H	100	100
5	$SiEt_3$	H	H	600	37
43	$SiEt_3$	$H_3CC{=}O$	H	600	34
44	$SiEt_3$	$H_3C(CH_2)_2C{=}O$	H	300	35
45	$SiEt_3$	$H_3C(CH_2)_2C{=}O$	$H_3C(CH_2)_2C{=}O$	40	4
46	$SiEt_3$	CH_3			3
47	$SiEt_3$		H	300	24

were more potent than the trans terminally substituted compounds. The relative lack of activity for analogues **56–59** might be attributed to the mode of delivery; these compounds may be active if administered subcutaneously.

Ongoing work in our laboratory is concerned with further variations in the alkyl substituents on silicon along with steroidal nuclear modifications to produce compounds having a more potent antifertility activity along with a greater separation from their estrogenic activity.

Experimental Section

Chemistry. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Spectral data (IR, Perkin-Elmer 137; NMR, Varian T-60, XL-100, or XL-400) were recorded for all compounds and were in accord with the assigned structures. Mass spectral data were obtained by using a CEC 21-110B high-resolution, double-focusing spectrometer. Microanalytical data were determined by Galbraith Labs, Knoxville, TN, for C and H and agreed to within ±0.04% of the calculated values. Woelm silica gel, activity III/30 mm, containing 0.5% fluorescent indicator, was used for all dry column chromatography,[17] with 5% EtOAc/$CHCl_3$ as the developing solvent unless otherwise stated. Tetrahydrofuran (THF) was dried by distillation from methylmagnesium bromide and stored over 4A molecular sieves.

Method A: 17α-[(Triethylsilyl)ethynyl]estradiol (5). To a stirred solution of 5 g of ethynyl estradiol (EE) in 185 mL of dry THF under nitrogen was added 20 mL of 3 M EtMgBr in ether. The reaction mixture was heated at 60 °C for 3 h and cooled to room temperature. Then 10 g of triethylchlorosilane was added. The reaction mixture was stirred at room temperature for 18 h, after which 5 mL of saturated NH_4Cl solution was added. Stirring was continued for 15 min, and then 150 mL of ether was added. The organic phase was separated, washed three times with water, and dried (Na_2SO_4). The solvent was removed at reduced pressure. The resulting oil was dissolved in 225 mL of 95% MeOH, and 0.5 mL of concentrated HCl was added. The mixture was stirred for 18 h at room temperature, and then the solvent was removed. Crystallization from CH_2Cl_2 gave 3.3 g of **5**. An analytical sample was prepared by recrystallization from CH_2Cl_2; mp 170–172 °C.

Method B: 17α-[(Diethylmethylsilyl)ethynyl]estradiol (34). To a stirred solution of 5.0 g of 17α-ethynylestradiol 3,17-bis(tetrahydropyranyl ether) in 250 mL of dry THF under nitrogen was added 4.6 mL of 2.3 M *n*-butyllithium in hexane. The reaction mixture was stirred for 1 h at room temperature followed by the addition of 1.6 g of trichloromethylsilane. After the mixture was stirred for an additional 1.5 h, ethyllithium in benzene (19.4 mL; 1.1 M) was added, and stirring was continued for 18 h. To the reaction mixture was added 200 mL of ether and 200 mL of saturated NH_4Cl. The ether layer was separated, washed with saturated NH_4Cl, and dried over Na_2SO_4. The solvent was removed at reduced pressure to afford 5.2 g of residue. The residue was dissolved in 100 mL of MeOH along with 10 drops of concentrated HCl and stirred for 6 h. The solvent was removed, and the resulting residue was dissolved in ether and washed with water. The ether phase was dried (Na_2SO_4) and evaporated to yield 3.8 g of crude **34**. The crude steroid was purified by dry column chromatography and recrystallized from MeOH to yield 1.21 g of **34**; mp 180–182 °C.

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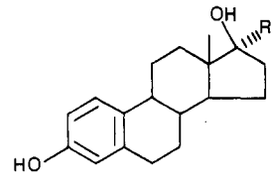
Table V. Oral Antifertility and Oral Estrogenic Potencies (Uterotropic) of Silyl-Substituted Estradiol Analogues Relative to EE in Rats



no.	R	antifertility[b] potency: *A*	estrogenic potency: *E*	separation *A*/*E*	purifn[c]	mp, °C	meth[d]	yield,[e] %
1	C≡CH	100	100					
48	$(SiMe_3)C{=}CH_2$	2	0.4	5	M	188–190	X	23
49	$CH{=}CHSiMe_3$ (*E*)	0 @ 10 mg/kg per day	0.2		M	195–198	X	25
50	$CH{=}CHSiMe_3$ (*Z*)	5	0.5	10	M	105–107	Y	29
51	$(SiEt_3)C{=}CH_2$	4	0.5	8	U, N	122–126	X	22
52	$CH{=}CHSiEt_3$ (*E*)	1.3	0.04	30	U, N	175–176	X	21
53	$CH{=}CHSiEt_3$ (*Z*)	10	0.5	20	U, L	127–129	Y	25
54	$[Si(n\text{-}Pr)_3]C{=}CH_2$	2	0.5	4	U, N	140–143	X	55
55	$CH{=}CHSi(n\text{-}Pr)_3$ (*E*)	0 @ 10 mg/kg per day	0.05		U, N	106–109	X	26
56	$[Si(n\text{-}Bu)_3]C{=}CH_2$	0 @ 5 mg/kg per day	0 @ 500 μg[a]		U, N	88–90	X	30
57	$CH{=}CHSi(n\text{-}Bu)_3$ (*E*)	0 @ 10 mg/kg per day	0 @ 1000 μg[a]		U	gum	X	21
58	$(SiPh_3)C{=}CH_2$	0 @ 5 mg/kg per day	0 @ 200 μg[a]		U, 0	142–144	X	37
59	$CH{=}CHSiPh_3$ (*E*)	0 @ 10 mg/kg per day	0 @ 200 μg[a]		U, N	136–138	X	27

[a] Testing was performed at Endocrine Labs unless otherwise noted as *a* for Mason Labs. [b] Minimum protective doses for prevention of pregnancy: 200 μg, Mason Labs; 100 μg, Endocrine Labs. [c] Purification: U, chromatography using neutral silica gel (mesh 70–230) and eluting with benzene/5% ether; L, recrystallization, hexane; M, recrystallization, methylene chloride; N, recrystallization, ether/hexane; O, recrystallization, benzene. [d] Methods A, B, and C, including reaction conditions, are described in the Experimental Section. [e] Yields were not maximized.

Method C: 17α-[[(1-Chloroethyl)dimethylsilyl]ethynyl]-estra-1,3,5(10)-triene-3,17β-diol (24). To 3.48 mL of (1-chloroethyl)trichlorosilane in 10 mL of dry THF at 0 °C was added, dropwise, 40.0 mL of 1.7 M methyllithium in ether. The reaction was stirred for 18 h at room temperature. To 4.64 g of ethynylestradiol 3,17-bis(tetrahydropyranyl ether) in 150 mL of dry THF, contained in a dropping funnel, was added 3.6 mL of 1.8 M *n*-butyllithium. The mixture was allowed to stand at room temperature for 2 h. Then the lithium acetylide derivative was added dropwise to the silane, with stirring at room temperature. After the reaction mixture was stirred for 18 h, it was poured into saturated NH_4Cl and ether. The ether was separated, washed with additional NH_4Cl, dried (Na_2SO_4), and evaporated. The residue was dissolved in 100 mL of MeOH containing 2.0 mL of 4% HCl and stirred for 18 h at room temperature. The MeOH was evaporated, and the residue was dissolved in ether. The ether phase was washed with water, dried (Na_2SO_4), and evaporated to afford 4.81 g of crude **24**. Purification by dry column chromatography and recrystallization from CH_2Cl_2 afforded 0.8 g of pure **24**; mp 175–176 °C.

17α-(3,3-Diethyl-1-pentynyl)estradiol (6). In a separatory funnel were placed 100 g of 3-ethyl-3-pentanol and 418 mL of concentrated HCl. The mixture was shaken vigorously several times during 1 h. The phases were allowed to separate, and the HCl layer was discarded. Fresh HCl was added and shaken with the triethylcarbinol as before. The triethylcarbinyl chloride was separated, dried ($CaCl_2$), and distilled, affording 67 g of the 3-chloro-3-ethylpentane; bp 78–79 °C (94 mm).

Vinyl chloride (46.2 g) was condensed, by means of a dry ice/acetone condenser, into a round-bottom flask at −70 °C (dry ice/acetone). The dry ice/acetone bath was removed, and the vinyl chloride was transferred to a stirred suspension of 67 g of 3-chloro-3-ethylpentane and 1.26 g of powdered aluminum chloride. After 1 h at −20 °C, the mixture was poured into cold 6 N HCl and extracted with ether. The ether phase was washed with water, dried (Na_2SO_4), and evaporated. The residue was quickly transferred to 1 L of vigorously stirred liquid ammonia containing 66.7 g of sodamide at −70 °C. The reaction mixture was stirred for 1 h at −70 °C and then allowed to warm to room temperature while the ammonia evaporated. To the residue was added 2 L of crushed ice followed by ether. The ether phase was separated, washed with water, dried (Na_2SO_4), and evaporated. The resulting oil was distilled to yield 14.8 g of 3,3-diethyl-1-pentyne; bp 78–82 °C (180 mm) (lit.[9b] 130 bp °C (760 mm)).

To a cold (0 °C) solution containing 21.7 mL of 3 M ethylmagnesium bromide in ether was added, over 30 min, a cold (0 °C) solution of 7.5 g of 3,3-diethyl-1-pentyne in 50 mL of dry THF. The reaction mixture was stirred at 0 °C for 0.5 h, at room temperature for 1 h, and finally at 60 °C for 1 h. To the reaction mixture was added 5.52 g of estrone 3-tetrahydropyranyl ether in 50 mL of dry THF. After the reaction mixture was stirred for 2 h at room temperature, it was heated to 60 °C for 16 h, after which it was cooled in an ice bath (0–5 °C) while saturated NH_4Cl and ether were added. The ether phase was separated, washed with water, dried (Na_2SO_4), and evaporated to yield 5.93 g of residue. The residue (2.0 g) was purified by dry column chromatography followed by recrystallization from MeOH to yield 0.8 g of **6**; mp 145.5–147 °C.

17α-[(Hydroxydiethylsilyl)ethynyl]estra-1,3,5(10)-triene-3,17β-diol (21). A solution of 0.050 g of **36** and 1.0 mL of a 2.5 M methanolic hydrochloric acid solution was stirred at room temperature for 14 days. The reaction mixture was poured into H_2O and extracted with ether. The ether solution was washed with additional H_2O and then dried over Na_2SO_4. The solvent was evaporated at reduced pressure to afford, after purification by thick-plate chromatography (benzene/10% ether solvent system), 0.011 g of **21**: NMR ($CDCl_3$) the multiplet signal at δ 4.0 for Si*H* of **36** was not observed; mass spectrum of di-Me_4Si derivative of **21**, *m*/*e* 542 (M).

17α-[(Diethylethynylsilyl)ethynyl]estra-1,3,5(10)-triene-3,17β-diol (42). Through 20 mL of THF at 0 °C was bubbled acetylene for 0.5 h. To this solution was added 0.83 mL of 3.0 M ethylmagnesium bromide in ether over 1.0 h. The solution was kept at 0 °C for 2.5 h. Meanwhile, in a dropping funnel containing 50 mL of THF were added sequential 1.2 g of ethynylestradiol bis(tetrahydropyranyl ether), 0.83 mL of 3.0 M ethylmagnesium bromide in ether, and 0.42 mL of diethyldichlorosilane. The resultant mixture was added to the above acetylene solution at 0 °C. The reaction mixture was allowed to warm to room temperature with stirring overnight and then poured into saturated NH_4Cl and extracted with ether. The ether phase was washed with saturated NH_4Cl and water, dried over Na_2SO_4, and evaporated to a solid, which was purified by silica gel preparative thick-plate chromatography. After development in 5% ether/benzene, 0.064 g of crystalline THP ether derivative of **42** was isolated. Hydrolysis of 0.060 g of this product in 0.2 mL of 2 N HCl and 3 mL of MeOH for 1 h yielded, after purification on preparative silica plates (25% ether/benzene), 15 mg of partially crystalline **42**. All attempts to crystallize **42** were unsuccessful; NMR ($CDCl_3$) δ 2.24 (s, 1 H, C≡C*H*).

17α-[(Triethylsilyl)ethynyl]estra-1,3,5(10)-triene-3,17β-diol 3-Acetate (43). Acetylation of 0.5 g of **5** in 1 mL of pyridine and

0.15 mL of acetic anhydride yielded, after the usual aqueous workup, 0.402 g of **43**; mp 129–130 °C.

17α-[(Triethylsilyl)ethynyl]estra-1,3,5(10)-triene-3,17β-diol 3-Butyrate (44). To a solution of 0.50 g of **5** in 50 mL of pyridine was added 3.5 mL of butyryl chloride. After the reaction mixture was stirred at room temperature under nitrogen for 1 h, the resulting suspension was diluted with $CHCl_3$, washed with water, and dried ($MgSO_4$). The solvent was removed under vacuum to yield 0.419 g of crude material. Separation on a silica gel column with chloroform followed by crystallization from ligroin afforded 0.138 g of **44**; mp 86–89 °C.

17α-[(Triethylsilyl)ethynyl]estra-1,3,5(10)-triene-3,17β-diol 3,17-Dibutyrate (45). To a solution of 2.0 g of **5** in 250 mL of dry THF was added 3.0 mL of 1.6 M butyllithium. The reaction mixture was stirred for 1 h at room temperature under nitrogen, and then 0.52 mL of butyryl chloride was added. After the reaction mixture was stirred for an additional 1.0 h, the solution was diluted with $CHCl_3$, washed with water, saturated $NaHCO_3$, and water, and then dried ($MgSO_4$). The solvent was evaporated to yield 2.10 g of crude product. Purification on preparative silica gel plates with 5% MeOH/$CHCl_3$ afforded 0.869 g of **45**, which would not crystallize. Lyophilization from benzene gave an analytical sample.

17α-[(Triethylsilyl)ethynyl]estra-1,3,5(10)-triene-3,17β-diol 3-Methyl Ether 17-Carbonylimidazole (46). To a solution of 0.556 g of [(triethylsilyl)ethynyl]estradiol 3-methyl ether in 30 mL of dry THF was added 0.8 mL of 1.6 M butyllithium in hexane. After the mixture was stirred at room temperature for 2 h, 1.65 g of carbonyldiimidazole was added and stirring was continued for 1 h. The reaction mixture was then diluted with $CHCl_3$, washed with water, and dried ($MgSO_4$). The solvents were removed under reduced pressure to yield 0.98 g of crude product. Separation on silica gel with chloroform as eluant gave 0.568 g of **46**. Crystallization from petroleum ether (bp 30–60 °C) gave 0.385 g of pure **46**; mp 112–114 °C.

17α-[(Triethylsilyl)ethynyl]estra-1,3,5(10)-triene-3,17β-diol 3-Cyclopentyl Ether (47). To a solution of 0.8 g of **5** in 15 mL of anhydrous EtOH were added 2.1 g of anhydrous K_2CO_3 and 1.7 mL of cyclopentyl bromide. The mixture was stirred under nitrogen for 7 days. The EtOH was evaporated and the residue dissolved in $CHCl_3$ and water. The organic phase was washed with 1 N HCl, water, and saturated NaCl and then dried (Na_2SO_4). The solvent was removed at reduced pressure. The crude product was purified on silica gel preparative plates developed with 7% EtOAc/$CHCl_3$, which led to the isolation of **47** as a pale-yellow oil (0.847 g), which did not crystallize.

Method X: 17α-[*trans*-(2-Triethylsilyl)vinyl]estradiol (52) and 17α-[(1-Triethylsilyl)vinyl]estradiol (54). To a solution of 8.5 g of EE in 150 mL of diglyme in a stainless steel bomb were added 0.2 g of 5% Pt/C and 4.56 mL of triethylsilane. The reaction mixture was heated to 160 °C for 16 h and then cooled to room temperature. The suspension was filtered through Celite, and the solvent was removed to afford 11.0 g of crude product. The mixture was purified on 250 g of neutral silica gel and eluted with a benzene/5% ether mixture to afford 5.0 g of **54**. An analytical sample was prepared by crystallization from ether/hexane; mp 122–126 °C. Further elution with benzene/5% ether afforded 4.45 g of **52**. An analytical sample was prepared by crystallization from ether; mp 175–176 °C.

Method Y: 17α-[*cis*-(2-Triethylsilyl)vinyl]estradiol (53). A 0.4-g sample of 17α-[(triethylsilyl)ethynyl]estradiol (**5**) in 20 mL of 95% ethanol with 0.025 mg of 5% Pd on $BaSO_4$ was hydrogenated with stirring at atmospheric pressure for 25 h. Filtration through Celite and evaporated of the solvent gave 0.4 g of residue. The product was separated by silica gel preparative TLC, eluting with benzene/15% ether, to afford 0.08 g of pure **53**. An analytical sample of **53** was prepared by crystallization from hexane: mp 127–129 °C.

Biology. Oral Estrogenic Activity. The estrogenic activity was determined by using immature female rats ovariectomized at 21 days of age. Ten rats were used per dose. Treatment was by oral administration of test compound for 4 days, beginning on the day of ovariectomy. The test compounds were diluted with a 0.5% (carboxymethyl)cellulose suspension. Animals were autopsied on the day following the last administration of test compound. Vaginal smears were obtained from animals that had open vaginas at the time of autopsy. The end points for comparison with a standard estrogen were an increase in uterine weight and cornification of vaginal smears.

Oral Antifertility Activity. Oral antifertility activity was determined by using rats. Adult cycling female rats selected were in the proestrous phase of the cycle. Treatment with test compound using 10 animals/dose began on the day of proestrus. Each female was caged overnight with two adult males. The findings of sperm in a vaginal smear obtained the following morning was used as evidence of insemination. Compounds were given once daily for a total of 8 days. The rats were sacrificed on the day following the last treatment, and the implantation sites and corpora lutea were counted.

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Potential Antitumor Agents. 48. 3′-Dimethylamino Derivatives of Amsacrine: Redox Chemistry and in Vivo Solid Tumor Activity

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Structure–activity relationships for a series of acridine-substituted 3′-$N(CH_3)_2$ derivatives of the clinical antileukemic drug amsacrine (**1**) are reported. The parent (unsubstituted) compound **3** has activity against the Lewis lung solid tumor that is superior to amsacrine (**1**), the new clinical amsacrine analogue **4**, and the recently developed 3′-$NHCH_3$ derivative **2**. Although the compounds generally bind less well to DNA and are less dose potent in vivo than either their amsacrine (3′-OCH_3) or 3′-$NHCH_3$ analogues, they show very high levels of antitumor activity, with the 4-OCH_3 derivative capable of effecting 100% cures of the Lewis lung solid tumor. The broad structure–activity relationships for acridine substitution more closely resemble those of the amsacrine than the 3′-$NHCH_3$ series, with 4-substituted and 4,5-disubstituted compounds showing the highest activity.

The DNA-intercalating 9-anilinoacridine derivative amsacrine (**1**) is a useful clinical antileukemic drug,[1,2] but has been shown to have only a narrow spectrum of clinical antitumor activity. Following extensive studies of structure–activity relationships for acridine-substituted analogues,[3-6] a "second-generation" compound (**4**; CI-921; NSC

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