exothermic reaction that developed initially had subsided, the mixture was refluxed for 2 hr, treated with Norit, and filtered hot. The filtrate on evaporation to dryness under reduced pressure furnished a colorless solid (9.5 g) which was recrystallized from a mixture of benzene and hexane; yield 6.2 g (60%).

All of the 5-bromomethyl compounds listed in Table I were prepared by essentially a similar procedure.

5-Chloromethyl-3-(3,4-dichlorophenyl)isoxazole (9, Table I).—Propargyl alcohol (2.8 g, 0.05 mole) was added in one lot, at room temperature, to a solution of 3,4-dichlorobenzonitrile oxide (0.05 mole) in ether (200 ml) with agitation. A vigorous exothermic reaction set in almost immediately at the termination of which the clear reaction mixture was refluxed for 2 hr, treated with Norit, and filtered hot. The filtrate was evaporated to dryness under diminished pressure and the 3-(3,4-dichlorophenyl)-5-hydroxymethylisoxazole thus obtained (7.9 g) was recrystallized from a mixture of ethyl acetate and hexane; colorless crystals, mp 105–106°, yield 6.5 g (62%).

Anal. Calcd for $C_{10}H_7Cl_2NO_2$: C, 49.19; H, 2.87. Found: C, 49.51; H, 2.95.

Thionyl chloride (15 ml) was added carefully to the well-dried and powdered 5-hydroxymethyl compound (5.0 g) contained in a flask fitted with a reflux condenser and $CaCl_2$ tube. A vigorous exothermic reaction resulted immediately and, after it had subsided, the mixture was warmed on the water bath for 30 min and cooled. Removal of the excess $SOCl_2$ *in vacuo* furnished an oily product which was dissolved in the required quantity of boiling hexane, treated with Norit, filtered hot, and cooled. The colorless **9** that separated was collected and recrystallized from the same solvent; yield 3.9 g (72%).

5-Chloromethyl-3-(4-chlorophenyl)isoxazole (**13**, Table I) was prepared by a similar method.

3-(3,4-Dichlorophenyl)-5-iodomethylisoxazole (2, Table I).—5-Bromomethyl-3-(3,4-dichlorophenyl)isoxazole (**5**, Table I; 2.6 g) was added to a warm solution of KI (5.0 g) in anhydrous dimethylformamide (50 ml), and the resulting mixture was heated on the water bath for 15 min and set aside for 3 hr at room temperature. It was then treated with crushed ice and water and the solid that separated was filtered, washed with water, air dried, and recrystallized from a mixture of benzene and hexane; colorless crystals, yield 2.5 g (71%).

The other two 5-iodomethyl derivatives listed in Table I (**4** and **7**) were obtained through a similar procedure.

Acknowledgment.—We wish to thank Professor T. R. Govindachari for his interest in this work, Dr. S. Selvavinayakam and his staff for the microanalysis, and Mr. C. N. Talaty for the preparation of some of the starting materials.

Syntheses and Properties of Mono-, Di-, and Tritestosteroxysilanes[1]

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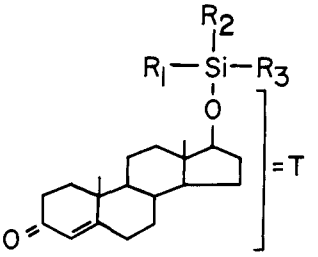
Silicon ethers are often highly lipid soluble, but tend to undergo slow hydrolytic cleavage to regenerate the free alcohols.[2] Introduction of a silicon ether linkage into a steroid alcohol may result in beneficial modifications in solubility as well as other properties of physiological interest.

This paper describes the preparation and properties of six novel testosteroxysilanes. Structural formulas are summarized in Figure 1.



R_1	R_2	R_3
CH_3	CH_3	CH_3
CH_3	T	CH_3
CH_3	T	T
C_6H_5	C_6H_5	C_6H_5
C_6H_5	T	C_6H_5
C_6H_5	T	T

Figure 1.—Structural formulas of testosteroxysilanes.

Experimental Section[3]

Testosteroxysilanes were prepared by treating testosterone with appropriate methylchloro- or phenylchlorosilanes in anhydrous benzene in the presence of anhydrous pyridine. The preparation of ditestosteroxydimethylsilane is described in detail as a model, and the preparations of the remaining five compounds are summarized in Table I.

Ditestosteroxydimethylsilane (II).—Testosterone (5.0 g, 0.018 mole) was dissolved in 75 ml of benzene containing pyridine (1.39 g, 0.018 mole). A solution of dimethyldichlorosilane (1.16 g, 0.009 mole) in 10 ml of benzene was added dropwise to the stirred testosterone solution. A white precipitate of pyridine hydrochloride formed at once. On completion of the addition, the funnel used in the process was rinsed with 10 ml of benzene. After the mixture was allowed to react at room temperature for 1 hr, it was gradually heated to reflux temperature and was maintained there for 5 hr. Then the mixture was cooled to room temperature, and the pyridine hydrochloride was removed by filtration. The clear filtrate was evaporated to dryness in a flash evaporator under reduced pressure and yielded a light yellow syrup (7.2 g). Upon adding anhydrous acetone (50 ml) to the syrup, a white precipitate was formed. Finally, 100 ml of acetone was added, and the precipitate dissolved after refluxing for 30 min. Standing overnight in the cold yielded 4.6 g (86%) of white needles. A second crop was harvested after reducing the volume of acetone.

Results

In all testosteroxysilanes, infrared absorption spectra showed elimination of the stretching frequency at 3500 cm^{-1} as a result of substitution of the C-17 β-OH group, and the simultaneous appearance of a strong absorption band at 1080–1065 cm^{-1}. The band at 1080–1065 cm^{-1} has been assigned to alkoxy-

(1) (a) This study was aided in part by Grant No. P-381 from the American Cancer Society to E. Chang. (b) The systematic name for testosterone is 17β-hydroxyandrost-4-en-3-one. The designation testosteroxysilane is used in the present paper as a general name for compounds containing testosterone nuclei and silicon connected by ether linkage. (c) The literature has recorded several trimethylsilyl derivatives of steroids used in facilitating the separation of steroid mixture by gas chromatography. Since these derivatives were prepared by a different method and were used without further characterization, they are not discussed in this paper.

(2) (a) E. G. Rochow, "An Introduction to the Chemistry of the Silicones," John Wiley and Sons, Inc., New York, N. Y., 1951; (b) R. H. Krieble and E. A. Burkhard, *J. Am. Chem. Soc.*, **69**, 2689 (1947).

(3) Infrared spectra were measured in KBr with a Perkin-Elmer Model 421 grating spectrophotometer. Melting points were determined with a Fisher-Adam hot stage apparatus and were corrected. Microanalyses were performed by the Galbraith Laboratories, Knoxville, Tenn. Bioassays were performed by Dr. E. G. Shipley, Endocrine Research Laboratory, Madison, Wis.

TABLE I

PREPARATION AND CHARACTERIZATION OF TESTOSTEROXYSILANE

Compd	Reaction at reflux (M) [hr][a]	Yield, g (%)	Mp, °C	% C Calcd	% C Found	% H Calcd	% H Found	% Si Calcd	% Si Found	ε (mμ) in EtOH
$C_{72}H_{96}O_3Si$ (I)	T-OH (0.017) + Py (0.019) + $(CH_3)_3SiCl$ (0.025) [2]	6.01 (96.4)	133–135	78.27	78.29	10.06	9.98	7.79	7.66	22,100 (240)
$C_{91}H_{130}O_4Si$ (II)	T-OH (0.018) + Py (0.018) + $(CH_3)_2SiCl_2$ (0.009) [5]	4.6 (86.0)	235–237	75.89	75.71	9.55	9.70	4.43	4.60	39,500 (240)
$C_{68}H_{84}O_6Si$ (III)	T-OH (0.01) + Py (0.01) + CH_3SiCl_3 (0.004) [2]	0.80 (26.9)	241–244	76.95	76.70	9.55	9.70	4.43	4.60	37,300 (240)
$C_{37}H_{62}O_2Si(C_6H_{12})$ (V)	T-OH (0.008) + Py (0.013) + $(C_6H_5)_3SiCl$ (0.008) [2]	3.5 (85.3)	60–90	81.93	81.99	8.75	8.56	4.32	4.40	15,600 (240) 39,100 (220)
$C_{50}H_{64}O_4Si$ (VI)	T-OH (0.007) + Py (0.007) + $(C_6H_5)_2SiCl_2$ (0.004) [12]	2.5 (96.0)	212–213	79.31	79.19	8.45	8.73	3.71	3.94	40,000 (240) 109,500 (220)
$C_{63}H_{86}O_6Si$ (VII)	T-OH (0.01) + Py (0.01) + $C_6H_5SiCl_3$ (0.004) [10]	3.3		78.21	73.66	8.60	8.42	2.90	4.15	---

[a] T-OH, testosterone; Py, pyridine.

TABLE II

STABILITIES OF TESTOSTEROXYSILANES IN WATER AND ALCOHOL

Compd	R_f[a]	Solvent	% recovered from chromatogram: Testosterone	% recovered from chromatogram: Starting compd
I	0.94	H_2O	88	12
		EtOH	85	15
II	0.86	H_2O	30	70
V	0.93	H_2O	0	100
VI	0.85	H_2O	25	75
		EtOH	38	62
Testosterone	0.32	...	..	...

[a] Values from paper chromatography.

Stability of Testosteroxysilanes in Water and Ethanol.—It is important to determine the ability of these compounds to resist hydrolysis as well as alcoholysis, since further biochemical studies will be made with them, and it is an inherent property of the Si–O–C bond in these compounds to undergo cleavage to regenerate free testosterone in hydrolytic solvents. Determinations were performed in triplicate. The general procedure was as follows. Samples (1 mg) were incubated with 10 ml of water or ethanol at 37° for 24 hr. Each incubation mixture was then extracted with methylene chloride, and the extract was subjected to separation by paper chromatography. Spots containing testosterone and unchanged testosteroxysilane were eluted, and their concentrations were estimated spectrophotometrically at 240 mμ. Results are summarized in Table II. The data suggest that unsymmetrical molecules like I are rapidly hydrolyzed to testosterone, whereas symmetrical molecules like II and VI are relatively stable. Unexpectedly, however, the unsymmetrical V was very stable in water. Its stability to resist hydrolytic cleavage may be attributed to stabilization of the Si–O–C bond by the concerted resonance action of the neighboring phenyl groups.

TABLE III

RESULTS OF BIOASSAY FOR TESTOSTEROXYSILANES

Compd (100 μg)	Body wt, g: Initial	Body wt, g: Final	mg ± SE (P)[a]: Ventral prostate	mg ± SE (P)[a]: Seminal vesicles	mg ± SE (P)[a]: Levator ani
Control	49	82	13.2 ± 0.29	10.7 ± 0.69	26.4 ± 1.93
Testosterone	48	88	55.8 ± 6.79 (*ca.* 0.001)	33.1 ± 5.33 (<0.01)	38.1 ± 2.28 (<0.02)
I	48	87	70.3 ± 1.79 (<0.001)	57.2 ± 2.48 (<0.001)	41.5 ± 3.85 (<0.02)
II	48	87	16.2 ± 0.92 (*ca.* 0.02)	11.6 ± 0.52 (NS)	30.7 ± 1.75 (NS)
III	47	85	24.9 ± 1.89 (*ca.* 0.001)	13.3 ± 0.40 (*ca.* 0.02)	30.3 ± 1.11 (NS)
V	49	85	17.6 ± 1.37 (*ca.* 0.02)	9.9 ± 0.40 (NS)	28.2 ± 1.50 (NS)
VI	48	84	14.8 ± 0.68 (>0.05)	8.5 ± 0.18 (*ca.* 0.02)	27.5 ± 1.27 (NS)
VII	49	81	38.8 ± 2.65 (<0.001)	15.2 ± 0.61 (<0.01)	29.2 ± 2.72 (NS)

[a] NS = not significant.

Bioassay of Testosteroxysilanes.—Androgenic and myotrophic activities of testosteroxysilanes were estimated in comparison with testosterone. The test materials, as well as testosterone, were given to 21-day-old castrated male rats by subcutaneous injection once a day for 7 days. Autopsies were performed the day after the last injection. Assay was performed on 5 animals/compound. The average values of weights, standard error, and probability are summarized in Table III. As is evident from this table the testosteroxysilanes studied, with the notable exception of I, did not exhibit any significant androgenic or myotro-

or aroxysilane Si–O–C bonds.[4] A small but characteristic band at 920–905 cm^{-1} has also been observed for all compounds of this series. According to Liu, *et al.*,[5] the absorption in the vicinity of 905 cm^{-1} is specific for the Si–O–C bond of siloxy steroid compounds.

Several attempts have been made at preparing tetratestosteroxysilane (testosterone orthosilicate), but in all instances the product could not be characterized. Reaction of testosterone and $SiCl_4$ in benzene and pyridine gave a glassy, foamy material as the product. This material was brittle and had a melting range of 52–90°.

Partition paper chromatography showed that all testosteroxysilanes are less polar than testosterone. The polarities of these compounds in the methylcyclohexane–ethylene glycol system were found to be in the following order: testosterone > III > II and VI > I and V.

(4) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co., Ltd., London.

(5) S. L. Liu, T. T. Wang, and H. L. Lin, *J. Chinese Chem. Soc.*, **11**, 62 (1964).

phic activities as manifested by changes in the weights of the ventral prostate, seminal vesicles, and levator ani. Interpretation of results obtained by this type of routine assay is necessarily very limited in scope because changes in histology and vital organs were not determined. Nevertheless, the fact that I was shown to be more active than testosterone may reflect rapid transportation of the compound across the lipid barrier and rapid cleavage to testosterone.

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Some Alkylideneaminooxyalkanoic Acids and Derivatives[1a]

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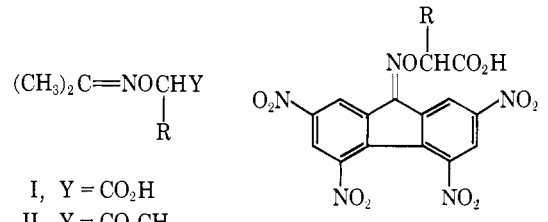
In view of the interest in alkylideneaminooxyacetic acids and their esters as potential therapeutic agents[2] and because of the use of alkylideneaminooxypropionic acids[3,4] in processes of optical resolution[3,5] and determination of absolute configuration,[6] we have now prepared additional homologs and their derivatives (I–IV) in this series. Several of these compounds have been tested for antitumor activity in the screening program of the Cancer Chemotherapy National Service Center. None of the compounds tested exhibited sufficient antitumor activity in a specific test system to meet the acceptance criteria of the CCNSC Protocols. Data on the screening tests are presented in Table I. Recrystallization from benzene of compounds IVb and IVc gives excellent products which are stable to drying *in vacuo* at moderate temperatures and which are 1:1 molecular compounds with the solvent. Benzene is lost if drying is conducted at higher temperatures.



I, Y = CO_2H
II, Y = CO_2CH_3
III, Y = CH_2OH

IV

a, R = CH_3
b, R = C_2H_5
c, R = $CH_3(CH_2)_3$

TABLE I
SUMMARY OF ANTICANCER SCREENING DATA[a]

Compd	Test[b] system	Dose, mg/kg	T/C,[c] %
Ib	SA	125	71
	LE	100	96
	LL	25[d]	103
	KB[e]		
Ic	SA	125	54
	LE	100	100
	LL	100	69
	KB[e]		
IIa	SA	125	115
	91	100	71
	LE	100	94
	KB[e]		
IIb	SA	60[f]	160
	LE	50	110
	LL	50	113
IIc	SA	125	109
	LE	100	101
	LL	100	102
IIIa	SA	125	66
	91	100	83
	LE	100	104
	KB[e]		
IIIc	SA	125	93
	91	100	121
	LE	100	109
	KB[e]		

[a] We are indebted to N. H. Greenberg of the Drug Evaluation Branch, CCNSC, National Cancer Institute, for assistance in interpretation of these data. For testing procedures and criteria for activity see *Cancer Chemotherapy Rept.*, **25**, 1 (1962). [b] SA = Sarcoma 180, LL = Lewis lung carcinoma, LE = L1210 lymphoid leukemia, 91 = S91 Cloudman melanoma, KB = tissue culture. [c] For LE, ratio of mean survival times of test animals to control animals. For other test systems, ratio of tumor weights of test animals to control animals. [d] Toxic in dosage of 100 mg/kg; survivors 0/6. [e] $ED_{50} > 0.01$ μg/ml. [f] Toxic in dosage of 125 mg/kg; survivors 3/6.

Experimental Section[7]

2-(Isopropylideneaminooxy)alkanoic Acids (I).—The procedure followed that used by Newman and Lutz[3] for the synthesis of Ia. From 500 g of 2-bromobutyric acid (Distillation Products Industries) and 219 g of acetoxime was obtained a liquid, bp 81–100° (0.5 mm), which crystallized on being dissolved in 50 ml of 30–60° petroleum ether–acetone (4:1, v/v) and cooling; yield 118 g (25%) of Ib, obtained as prisms, mp 48–52°, raised to 54.5–55.5° on repeated recrystallization from the same solvent.

Anal. Calcd for $C_7H_{13}NO_3$: C, 52.81; H, 8.23; N, 8.80. Found: C, 52.81; H, 8.18; N, 8.80.

Similarly 2-bromohexanoic acid was converted to Ic and crystallized from petroleum ether–acetone (5:3, v/v) to give prisms (13% yield), mp 41–43.5°, raised to 42–43.5° on recrystallization from petroleum ether alone.

Anal. Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.61; H, 9.13; N, 7.78.

Methyl 2-(Isopropylideneaminooxy)alkanoates (II).—The procedure followed that used by Klemm, Stalick, and Bradway[6] for

(1) (a) This investigation was supported by research grants (CY-3097 and CA-5969) from the National Cancer Institute, U. S. Public Health Service. (b) Research Assistant, 1961–1963.

(2) A. Richardson, *J. Med. Chem.*, **7**, 824 (1964).

(3) M. S. Newman and W. B. Lutz, *J. Am. Chem. Soc.*, **78**, 2469 (1956).

(4) P. Block, *J. Org. Chem.*, **30**, 1307 (1965).

(5) M. S. Newman and D. Lednicer, *J. Am. Chem. Soc.*, **78**, 4765 (1956); L. H. Klemm and D. Reed, *J. Chromatog.*, **3**, 364 (1960); L. H. Klemm, K. B. Desai, and J. R. Spooner, *ibid.*, **14**, 300 (1964).

(6) L. H. Klemm, W. Stalick, and D. Bradway, *Tetrahedron*, **20**, 1667 (1964).

(7) Melting points were taken in capillary tubes by means of a stirred oil bath and are corrected. Infrared spectra were determined by means of a Perkin-Elmer Model 137 spectrophotometer. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.