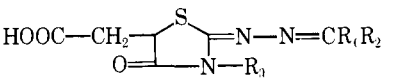
TABLE II
PROPERTIES OF COMPOUNDS PREPARED



Compd	R_1	R_2	R_3	Yield, %	Mp, °C	Formula	Calcd, % C	H	N	S	Found, % C	H	N	S
1[a]	C_6H_5	CH_3	H	80	248–249	$C_{13}H_{13}N_3O_3S$	53.61	4.50	14.43	10.98	53.82	4.76	14.16	11.16
2[b]	C_6H_5	CH_3	C_6H_5	76	188–189	$C_{19}H_{17}N_3O_3S$	62.11	4.66	11.44	8.70	61.85	4.62	11.26	8.62
3[c]	C_6H_5	CH_3	p-$CH_3C_6H_4$	88	219–220	$C_{20}H_{19}N_3O_3S$	62.98	5.02	11.02	8.38	62.96	5.24	10.73	8.56
4	C_6H_5	CH_3	p-$CH_3OC_6H_4$	86	216–218	$C_{20}H_{19}N_3O_4S$	60.45	4.82	10.58	8.05	60.20	4.86	10.68	8.38
5[d]	C_6H_5	C_2H_5	H	81	228–229	$C_{14}H_{15}N_3O_3S$	55.08	4.45	13.77	10.48	55.30	4.77	13.92	10.04
6	C_6H_5	C_2H_5	p-$CH_3C_6H_4$	82	179	$C_{20}H_{21}N_3O_3S$	62.65	5.52	10.96	8.43	62.87	5.49	10.45	8.83
7	p-$(CH_3)_2NC_6H_4$	H	H	78	263–264	$C_{14}H_{16}N_4O_3S$	52.42	5.04	17.49	9.99	52.45	5.14	17.32	10.25
8	2-Furyl	H	H	85	250	$C_{10}H_9N_3O_4S$	44.95	3.40	15.73	11.98	44.76	3.48	15.50	12.31
9	2-Furyl	H	p-$CH_3C_6H_4$	76	230	$C_{17}H_{15}N_3O_4S$	57.14	4.23	11.76	8.96	57.31	4.56	12.17	8.96

[a] λ_{max}^{EtOH} 294 mμ (ε 19,400). [b] λ_{max}^{EtOH} 295 mμ (ε 19,300). [c] λ_{max}^{EtOH} 296 mμ (ε 18,350). [d] λ_{max}^{EtOH} 295 mμ (ε 18,350).

Anal. Calcd for $C_{17}H_{19}N_3S$: C, 68.66; H, 6.44; N, 14.13. Found: C, 68.45; H, 6.38; N, 14.20.

Derivatives of 5-Carboxymethylthiazolidine-2,4-dione. General Procedure.—Equimolecular amounts of the corresponding thiosemicarbazones and maleic anhydride (usually 0.01 mole) were suspended in 40 ml of benzene (or toluene), and the mixture was refluxed for 2 hr. Upon cooling to room temperature, the product was filtered off, washed with the solvent employed in the reaction, dried, and crystallized from ethanol. The compounds with the corresponding analytical data are presented in Table II.

3-Aryl-5-halomethylisoxazoles. A New Class of Anthelmintics

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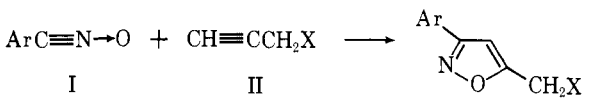
Received December 8, 1965

Isoxazoles have been reported to possess diverse biological activities[1] but to date there is no reference, in the literature, to any isoxazole having anthelmintic activity. In our continuing efforts to find suitable drugs for tapeworm, pinworm, and hookworm infections, we had occasion to synthesize 4-bromomethyl-3-(4-chlorophenyl)isoxazole (**1**, Table I) and subject it to anthelmintic screening. While it was devoid of any activity against oxyurids and *Nematospiroides* infections in mice, it exhibited pronounced activity against *Hymenolepis nana* infection when administered orally. Accordingly, 14 analogs of this compound (see Table I) were prepared and examined for anthelmintic activity.

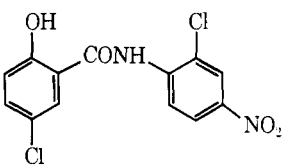
Chemistry.—The 3-aryl-5-bromomethylisoxazoles (IIIc) were prepared by the dipolar cycloaddition of various benzonitrile oxides (I) to propargyl bromide (II, X = Br) essentially according to the procedure of D'Alcontres and Lo Vecchio.[2] These could be converted smoothly into the corresponding 5-iodomethyl derivatives (IIId) by treatment with potassium iodide in anhydrous dimethylformamide. The 5-chloromethyl analogs (IIIb) were obtained by the action of thionyl chloride on the respective 5-hydroxymethyl derivatives (IIIa) which were in turn prepared by treating benzonitrile oxides (I) with propargyl alcohol (II, X = OH).[3] Compounds of the type IIIb can also be prepared directly by the cycloaddition of benzonitrile oxides (I) to propargyl chloride (II, X = Cl)[4] (see Scheme I).

SCHEME I



I II

IIIa, X = OH
b, X = Cl
c, X = Br
d, X = I



IV

Biology.—Swiss albino mice of either sex weighing approximately 20 g each were used in all the experiments. Each animal was experimentally induced to *H. nana* and *N. dubius* infections. Oxyurid infections due to *Syphacia obvelata* and *Aspicularis tetraptera* occurred naturally.

Viable *H. nana* eggs were obtained from the gravid segments of worms harbored by the untreated mice and counted in three 0.1-ml samples following the technique of Standen.[5] Infective *N. dubius* larvae were obtained according to the method of Sheffield, *et al.*[6] A suspension of these larvae was mixed with one of *H. nana* eggs in such proportions as to furnish a final mixture with concentrations of 250–300 larvae/ml and 5000–6000 eggs/ml. Each mouse was administered 0.2 ml of this suspension by gavage.

The infected mice were randomly divided into treated and control groups. On the 19th or 20th day postinfection, the mice in the test groups were treated

(1) (a) A. Quilico in "The Chemistry of Heterocyclic Compounds," Vol. 15, R. H. Wiley, Ed., Interscience Publishers, Inc., New York, N. Y., 1962, p 233; (b) N. D. Kochetkov and S. D. Sokolov, *Advan. Heterocyclic Chem.*, **2**, 365 (1963).

(2) G. S. D'Alcontres and G. Lo Vecchio, *Gazz. Chim. Ital.*, **90**, 1239 (1960).

(3) E. Mugnani and P. Grünanger, *Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat.*, **14**, 95 (1953); *Chem. Abstr.*, **48**, 2685 (1954).

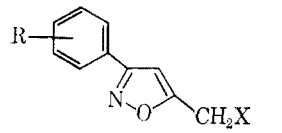
(4) G. S. D'Alcontres and G. Cuzzocrea, *Atti Soc. Peloritana Sci. Fis. Mat. Nat.*, **3**, 179 (1956); *Chem. Abstr.*, **52**, 1994 (1958).

(5) O. D. Standen, *Exptl. Chemotherapy*, **1**, 701 (1963).

(6) H. G. Sheffield, J. E. Meisenhelder, and P. E. Thompson, *J. Parasitol.*, **45**, 653 (1959).

TABLE I

3-ARYL-5-HALOMETHYLISOXAZOLES



Compd	R	X	Mp, °C	Recrystn solvent[a]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Dose, mg/kg *po* × no. of days	Activity against *H. nana* (mice) cleared/treated
1	4-Cl	Br	118–120	B–H	$C_{10}H_7BrClNO$	44.06	2.59	5.14	43.99	2.51	5.33	300 × 3	10/10
2	3,4-Cl_2	I	99–101	H	$C_{10}H_6Cl_2INO$	33.93	1.71	3.96	34.44	1.47	4.24	400 × 3	10/10
3	H	Br	92–93[b]	P	$C_{10}H_8BrNO$	50.50	3.44		50.45	3.39		300 × 3	4/ *C*
4	3-NO_2	I	117–119	E–H	$C_{10}H_7IN_2O_3$	36.39	2.14	8.49	36.59	2.57	9.07	400 × 3	9/10
5	3,4-Cl_2	Br	94–96	B–P	$C_{10}H_6BrCl_2NO$	39.13	1.97		39.16	1.97		400 × 3	8/10
6	4-Cl-3-NO_2	Br	103–107	M	$C_{10}H_6BrClN_2O_3$	37.81	1.91	8.82	38.00	1.91	8.97	400 × 3	8/10
7	4-Cl	I	108–110	H	$C_{10}H_7ClINO$	37.58	2.21	4.38	37.61	2.22	4.72	400 × 3	8/10
8	3,4-Cl_2-5-NO_2	Br	78–80	E–H	$C_{10}H_5BrCl_2N_2O_3$	34.12	1.43		34.18	1.38		400 × 3	8/9
9	3,4-Cl_2	Cl	72–74	P	$C_{10}H_6Cl_3NO$	45.75	2.31	5.34	46.07	2.66	5.09	400 × 3	3/10
10	4-Br	Br	134–136	B–P	$C_{10}H_7Br_2NO$	37.89	2.23	4.42	38.02	2.19	4.17	400 × 3	3/5
11	2,4-Cl_2	Br	61–62	P	$C_{10}H_6BrCl_2NO$	39.12	1.97	4.56	39.17	2.02	4.17	400 × 3	4/10
12	3-F	Br	69–71	H	$C_{10}H_7BrFNO$	46.90	2.76	5.47	47.22	2.86	5.29	400 × 3	1/5
13	4-Cl	Cl	101–104	B–H	$C_{10}H_7Cl_2NO$	52.65	3.10	6.14	52.50	3.32	5.61	400 × 3	1/10
14	3-NO_2	Br	83–85	H	$C_{10}H_7BrN_2O_3$	42.41	2.49	9.89	42.37	2.74	9.58	400 × 3	0/5
15	4-F	Br	74–75	H	$C_{10}H_7BrFNO$	46.90	2.76	5.47	47.19	2.99	5.51	100 × 3	0/5[d]

[a] P = petroleum ether (bp 40–60°), M = methanol, B = benzene, H = hexane, E = ethyl acetate. [b] Lit.[2] mp 88°. [c] Toxic at 300 mg/kg *po*. [d] Toxic at higher doses.

orally with the test compounds at varying doses in 10 ml/kg of sterile physiological saline containing 0.05% Tween 80 as a vehicle. N-(2-Chloro-4-nitrophenyl)-5-chlorosalicylamide (IV)[7] was used as the reference drug and administered in a similar fashion. The animals in the control group received the vehicle only.

All animals in both the treated and control groups were fasted on the second day and sacrificed on the third day following a single-dose treatment while the animals treated with three doses were starved on the third day and sacrificed on the fourth day. The entire small intestine, cecum, and colon of each mouse were collected separately in Petri dishes containing tap water, incised lengthwise, and examined under the microscope (10×) carefully for worms including the scolices of *H. nana*. Results were determined on an all or none basis. The compound showing a 100% clearance of *H. nana* at 300 mg/kg was further studied in mice using a pure infection with the same dose of inoculum as indicated earlier.

Of the 14 analogs tested against *N. dubius*, *H. nana*, and oxyurid worms in mice, the first ten showed moderate to strong activity against *H. nana* when used in a daily dose of 400 mg/kg on three successive days but the rest of the compounds had poor or no activity (see Table I). 5-Bromomethyl-3-(4-chlorophenyl) isoxazole (**1**, Table I) was the most active. The comparative activity on an all or none basis from single or multiple doses of this compound and of the reference drug is summarized in Table II. The results of this test group indicate that **1** was active at 300 mg/kg/day for three successive days against *H. nana* since neither worms nor their scolices were present at autopsy. In single doses an absolute cure was obtained at 800 mg/kg. In similar tests, IV caused a 100% clearance of *H. nana* in a daily dose of 150 mg/kg on three successive days or in a single dose of 400 mg/kg. The test compounds were, however, inactive against *N. dubius* and oxyurid worms in mice at 300 mg/kg or higher doses.

(7) Marketed by Farbenfabriken Bayer A. G. (West Germany) as Yomesan®.

TABLE II

EFFICACY OF 5-BROMOMETHYL-3-(4-CHLOROPHENYL)ISOXAZOLE (1, TABLE I) AND N-(2-CHLORO-4-NITROPHENYL)-5-CHLOROSALICYLAMIDE (IV)[7] IN SINGLE AND MULTIPLE DOSES AGAINST *H. nana* INFECTION IN MICE

Compd	Dose, mg/kg day	No. of doses	Mice cleared	% clearance	LD_{50}, mg/kg *po* (mice)
1	100	3	5/10	50	6081 ± 22.46
	200	3	14/20	70	
	300	3	10/10	100	
	400	1	10/25	40	
	600	1	11/15	73	
	800	1	5/5	100	
IV	100	3	12/15	80	>3000
	150	3	10/10	100	
	200	1	8/15	53	
	300	1	11/15	73	
	400	1	5/5	100	
Control	...	..	3/30	10	

From the results it appears that some of the compounds of the isoxazole series listed in Table I possess marked cestocidal properties. Of these, **1** is the most active but it is only half as potent as IV at similar doses. It is not clear how **1** exerts its antitapeworm activity *in vivo* but our studies *in vitro* indicate that the action is direct on the parasite since a concentration of 10^{-4} g/ml is powerful enough to kill the worms in less than 3 hr at 37°. The activity of **1** against *H. nana* indicates that this and related compounds may be useful cestocidal agents. Further work in this direction is in progress.

Experimental Section[8]

Preparation of Ethereal Solutions of Nitrile Oxides.—A solution of the appropriate benzhydroxamoyl chloride (0.05 mole) in ether (200–250 ml) was extracted thoroughly with a cold aqueous solution of 4% NaOH (50 g) and the ether layer containing the nitrile oxide was removed, washed with a small quantity of ice water, dried ($CaCl_2$), and used immediately.

5-Bromomethyl-3-(4-chlorophenyl)isoxazole (1, Table I).—Propargyl bromide (11.9 g, 0.1 mole) was added in one lot, at room temperature, to a solution of 4-chlorobenzonitrile oxide (0.1 mole) in ether (300 ml) with agitation. After the vigorous

(8) Melting points were determined in open capillary tubes and are uncorrected.

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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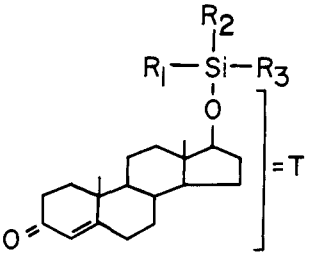
Received September 27, 1965

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.