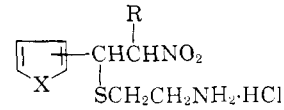
TABLE II

PHYSICAL CONSTANTS, ANALYTICAL DATA, AND ANTIFUNGAL ACTIVITIES OF HETEROCYCLIC DERIVATIVES

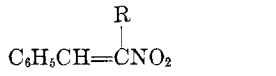


Side chain position	Substituents X	Substituents Ring	Substituents R	M.p., °C.	Formula	Chlorine, % Calcd.	Chlorine, % Found	Ref. to nitrostyrene	Lowest level of inhibition, γ/ml. *C. albicans*	*T. mentagrophytes*	*C. ulmi*
2	S	5-C_2H_5	H	131–132	$C_{10}H_{16}N_2O_2S_2 \cdot HCl$	11.95	12.47, 12.38	*a*	1000	40	250
2	S	None	CH_3	125–128	$C_9H_{14}N_2O_2S_2 \cdot HCl$	12.54[b]	12.77[b]	*a*	>1000	10	1000
2	S	5-Cl	H	157–161 dec.	$C_8H_{11}ClN_2O_2S_2 \cdot HCl$	23.38	23.49	*a*	>1000	40	50
3	S	None	H	141–142	$C_8H_{12}N_2O_2S_2 \cdot HCl$	13.19	13.48	*c*	>1000	1000	100
2	O	None	H	139–140	$C_8H_{12}N_2O_3S \cdot HCl$	*d*	*d*	*e*	1000	40	1000

[a] W. J. King and F. F. Nord, *J. Org. Chem.*, **14**, 405 (1949). [b] Ionic Cl. [c] E. E. Campaigne and W. C. McCarthy, *J. Am. Chem. Soc.*, **76**, 4466 (1954). [d] Sulfur: calcd., 12.69; found, 12.54. [e] J. Thiele and H. Landers, *Ann.*, **369**, 300 (1909).

TABLE III

NEW NITROSTYRENES



Substituents Ring	Substituents R	M.p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found
2-Cl, 5-NO_2	CH_3	64–67	14.62	14.58
2-Cl, 5-NO_2	C_2H_5	40–52	10.92	10.72
2,6-Cl_2	C_2H_5	Oil	5.69	5.39
2,6-Cl_2, 3-NO_2	C_2H_5	102–106	9.63	9.76
2,4-$(CH_3)_2$	H	119–126[a]	7.91	7.62

[a] Boiling point (0.2 mm.).

butene which was added to 100 ml. of fuming HNO_3 with stirring. The temperature of the reaction rose to 40–45°. Stirring was continued for 3 hr. and then the solution was poured onto ice. The mixture was extracted with CH_2Cl_2 and the extracts were dried and concentrated. When methanol was added to the residue, a solid formed which was separated by filtration to yield 15.9 g. of the title compound, m.p. 102–106°.

Testing.—Qualitative tests with the bacteria, the fungi, and the alga were run by placing about 5 mg. of each compound directly on the surface-inoculated agar in 100 × 20 mm. Petri dishes. These were incubated at room temperature or 37°, depending on the requirements of the test organism, until growth was satisfactory. Antibiotic activity was indicated by the presence of a clear zone surrounding a compound due to failure of the organism to grow in this area. Nutrient agar was used for *B. subtilis* and *E. coli*, blood agar base containing 5% defibrinated rabbit blood for *D. pneumoniae*, and beef extract agar for *E. carotovara*. The fungi were cultivated on Sabouraud dextrose agar and *C. vulgaris* on modified Bristol agar. The latter organism was grown under continuous fluorescent illumination. *Tetrahymena geleii* was cultured in proteose peptone–sucrose broth for 24 hr. at room temperature and then transferred aseptically in 0.5-ml. quantities to sterile 13 × 100 mm. test tubes to which about 5 mg. of the individual compounds had been added. Incubation was continued for 24 hr., and the degree of growth was determined by microscopic examination of the cultures.

The quantitative tests with *C. albicans*, *T. mentagrophytes*, and *C. ulmi* were run in Sabouraud dextrose agar. The test compounds were dissolved in the hot agar and then diluted serially in test tubes. These were permitted to cool in a vertical position and the test organisms were inoculated onto the surface of the agar. Following a suitable incubation period, the presence or absence of growth was determined by visual inspection.

Acknowledgment.—The authors thank A. R. Zigman, Richard Salzmann, and Russell Reuter, and especially Ivar Laos for the preparation of initial or larger amounts of a number of these compounds.

Phosphorylated Benzenesulfonamides as Animal Systemic Insecticides[1]

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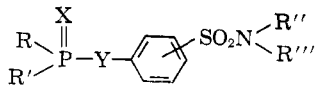
Received November 14, 1964

A number of phosphorylated benzenesulfonamides (I) are active as anthelmintics and animal systemic insecticides, as well as plant insecticides. Animal systemic activity (mouse–mosquito test) and mouse toxicity data are presented and structure–activity relationships are discussed. The most active compounds are phosphates and phosphorothionates with *para*-positioned sulfamoyl groups, the sulfamoyl group being substituted by hydrogen, lower alkyl, or acyl groups.

A number of phosphorylated benzenesulfonamides have been prepared of general structure I, where R and



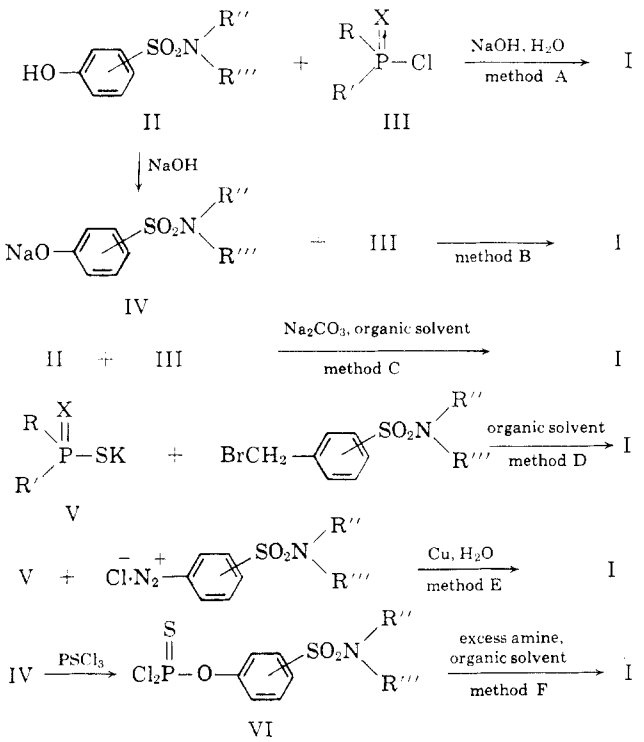
R′ are alkoxy, alkyl, alkylamino, methylthio, phenyl, chloro, or *p*-sulfamoylphenoxy; R″ and R‴ are hydrogen, alkyl, aryl, heterocyclic, or acyl; X is O or S; and Y is O, S, NH, or SCH_2. Members of this series exhibit activity as plant insecticides[2] and animal systemic insecticides and anthelmintics. A number of these compounds have particular utility in the animal systemic area since they combine high insecticidal activity

(1) Presented in part at the 140th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1961; Abstracts of Papers, p. 27-O.

(2) R. G. Dent and L. P. Ditman, *J. Econ. Entomol.*, **57**, 177 (1964); G. Guyer and A. Wells, Proceedings of the Entomological Society of America North Central Branch, **18**, 49 (1963); R. Redfern, M. Cleveland, and D. Hamilton, *ibid.*, **18**, 88 (1963).

with relatively low mammalian toxicity. Representative of this type of active compound is O,O-dimethyl O-*p*-(dimethylsulfamoyl)phenyl phosphorothioate[3] (Table I, **14**), for which considerable data have been reported.[4] This insecticidal drug is effective against the grubs *Hypoderma lineatum* and *H. bovis*, important internal parasites of cattle, when administered orally, dermally, or parenterally. This paper reports the synthesis and animal systemic insecticidal test data for a series of phosphates, phosphorothioates, phosphorodithioates, phosphoramidothioates, and other compounds of type I. For ease of manipulation, the series has been subdivided into four structural types and presented in the corresponding Tables I–IV. In some cases previously unreported intermediates were prepared; these compounds are tabulated in Table V. Some members of the series of phosphorylated benzenesulfonamides have been reported in the patent literature.[5]

The phosphorylations were carried out by six general methods, as outlined in the following diagram. (Two syntheses not conforming to these general methods are indicated in the tables and reported in the Experimental section.) Method A was used to prepare most of the phosphorothioates I (X = S; Y = O). In those cases where the sodium salts of the phenolsulfonamides IV were available, method B was employed and gave comparable yields of products. In the initial work using



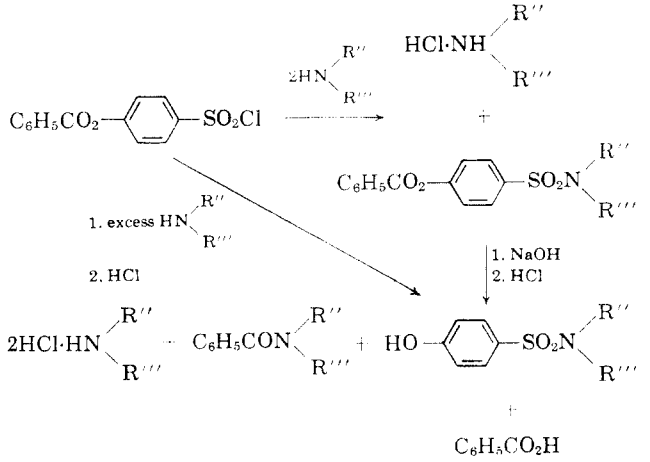
method A, the phenolsulfonamide II was dissolved in aqueous base and the phosphorochloridothioate III was added rapidly. Generally an excess of base was then added, either in one portion or over a relatively short period of time, to keep the reaction mixture alkaline. It was later found that significant improvement in yield could be obtained by using an excess of chloridate over phenolsulfonamide.

Because of hydrolytic instability, the phosphates I (X and Y = O; R and R′ = alkoxy) were prepared by the nonaqueous method C. Yields in most cases were low, due to difficulties encountered during purification procedures. Many attempts to use method A for the phosphates either failed completely or gave extremely low yields of product, with the single exception of **27** (Table II). This compound was prepared using excess chloridate as described above for the phosphorothioates.

The phosphorylated sulfamoylbenzyl compounds I (Y = SCH_2) were prepared in relatively high yields using method D. Reaction of potassium phosphorodithioates V (X = S) with aqueous solutions of diazonium salts, method E, gave phosphorodithioates I (X and Y = S). Yields were generally poor because of purification difficulties. Method F gave phosphoramidates I (R and R′ = alkylamino). Difficulties were encountered in isolation of the dichloridates VI; thus, in some cases crude dichloridate was used, resulting in very low yields of I. Methods of preparation of the remaining compounds of the series are indicated in the tables.

The phosphorylated benzenesulfonamides were generally obtained as low-melting (<100°) solids or very high-boiling liquids. In some cases, the liquids were distilled, but purification was generally effected by column adsorption chromatography on acid-washed, activated alumina. Recovery was good except in the case of the phosphates I (X and Y = O; R and R′ = alkoxy). For these materials, the use of alumina in most cases resulted in extensive decomposition of the sample. The use of silica gel adsorbents did not afford an appreciable improvement. The best method found was to elute rapidly through an alumina column, allowing the material to remain on the column no longer than 3 or 4 hr. Using this procedure, recovery was good and decomposition negligible.

Most of the intermediate 1-phenol-4-sulfonamides have been reported in the literature. Those compounds which are new are reported in Table V and were obtained by two methods.



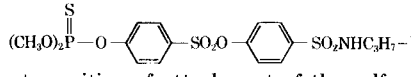
Both methods of preparation were employed for the majority of the compounds, with the emphasis in the initial work placed on the two-step route, involving for-

(3) This compound has been given the generic name famphur. It was previously referred to as CL 38,023 and famophos.

(4) For example: (a) R. O. Drummond, *J. Econ. Entomol.*, **56**, 632 (1963); (b) A. Hill, Jr., F. W. Knapp, and H. Knutson, *ibid.*, **56**, 390 (1963); (c) W. W. Neel, C. L. Blount, and W. W. Kilby, *ibid.*, **56**, 101 (1963); (d) J. H. Drudge and J. Szanto, *Am. J. Vet. Res.*, **24**, 337 (1963); *J. Parasitol.*, **48**, 28 (1962); (e) E. C. Turner, Jr., D. F. Watson, and F. S. McClaugherty, *J. Am. Vet. Med. Assoc.*, **141**, 360 (1962); (f) I. B. Wood, J. E. Emro, and E. Waletzky, *J. Parasitol.*, **47**, 36 (1961).

(5) (a) G. Berkelhammer, U. S. Patents 3,005,002 and 3,005,004 (1961); (b) E. Scheck and G. Schrader, German Patent 1,039,070 (1958).

TABLE I: O,O-DIALKYL O-SULFAMOYLPHENYL PHOSPHOROTHIOATES $(R^1O)_2P(O)-O-C_6H_4-SO_2NR^2R^3$

Compd.	Isomer[a]	R^1	R^2	R^3	M.p., °C.,[b] or $n^{25}D$[c]	Recrystn. solvent[d]	Yield,[e,f] %	Formula	Calcd., % C	H	N	P	S	Found, %[g] C	H	N	P	S	Biological data,[h] mg./kg. ED_{50}	LD_{50}
1	2	CH_3	H	H	79–80	T	29	$C_8H_{12}NO_5PS_2$	32.32	4.06	4.71	10.42	21.58	32.61	4.85	4.71	10.50	21.22	>100	>100
2	3	CH_3	H	H	52–53	T	30	*i*						32.39	4.06	4.60	10.34	21.48	>100	>100
3	4	CH_3	H	H	70–72	T	54	*i*						32.23	4.00	4.54	10.02	21.75	0.05	45
4	4	CH_3	H	CH_3	36–38	T–Hx	61	$C_9H_{14}NO_5PS_2$	34.72	4.53	4.50	9.95	20.60	34.63	4.50	4.40	9.92	20.72	0.1	15
5	4	CH_3	H	C_2H_5	1.5392		36	$C_{10}H_{16}NO_5PS_2$	36.92	4.96	4.31	9.52	19.71	37.21	5.11	4.36	9.81	19.78	0.2	65
6	4	CH_3	H	C_3H_7-*i*	1.5359		21	$C_{11}H_{18}NO_5PS_2$	38.93	5.34	4.12	9.13		38.83	5.28	4.28	8.79		0.1	94
7	4	CH_3	H	C_4H_9-*n*	1.5331		24	$C_{12}H_{20}NO_5PS_2$	40.77	5.70	3.96	8.77	18.14	40.59	5.71	3.92	8.89	18.35	5	10–100
8	4	CH_3	H	C_4H_9-*t*	58.5–59	B–Hp	34	*j*						40.36	6.12	3.89	8.40	17.72	>100	>100
9	4	CH_3	H	C_6H_4Cl-*p*	87–88	B–Hx	22	$C_{14}H_{16}ClNO_5PS_2$	41.23	3.71	3.44	7.60	8.69[k]	41.47	3.73	3.57	7.46	8.76	100	>100
10	4	CH_3	H	$COCH_3$	142–144	T	68	$C_{10}H_{14}NO_6PS_2$	35.39	4.16	4.15	9.13	18.90	35.24	4.50	4.22	9.17	18.83	0.4	>100
11	4	CH_3	H	COC_3H_7-*i*	103–104.5	Ca	32	$C_{12}H_{18}NO_6PS_2$	39.22	4.94	3.81	8.43	17.45	39.13	4.98	3.73	8.49	17.33	<1.0	>100
12	4	CH_3	H	COC_6H_5	102–104	T	63	$C_{15}H_{16}NO_6PS_2$	44.88	4.02	3.49	7.72	15.98	45.06	4.01	3.54	7.66	15.97	12	>100
13	4	CH_3	H		178.5–180	Ea	41	$C_{11}H_{13}N_2O_5PS_3$	34.72	3.44	7.35	8.15	25.29	34.98	3.52	7.35	8.10	29.96	>100	>100
14	4	CH_3	CH_3	CH_3	52.5–53.5	T–Hx	27	*l*						36.83	5.05	4.32	9.57		0.4	30
15	4	CH_3	C_2H_5	C_2H_5	82–83	Hx	68	*j*						40.86	5.95	4.00	8.80	18.24	1–2.5	>100
16	4	CH_3	$-(CH_2)_4-$		60–61.5	B–Hx	22	$C_{12}H_{18}NO_5PS_2$	41.02	5.16	3.99	8.82	18.25	40.78	5.47	4.02	8.91	18.48	>10	50
17	4	CH_3	$-(CH_2)_2O(CH_2)_2-$		68–69.5	Ma[m]	28	*n*						39.29	5.00	3.72	8.22	17.11	>50	5–25
	3	C_2H_5	H	H	53.5–54.5	T–Hx	17	*l*						37.12	5.02	4.17	9.45	19.50	>100	>100
9	4	C_2H_5	H	H	1.5394		56	*l*						36.71	4.94	4.17	9.45	19.69	0.5	20
20	4	C_2H_5	H		131–132	Ea	10	$C_{13}H_{17}N_2O_5PS_3$	38.23	4.20	6.86	7.58	23.55	38.10	4.24	6.56	7.56	23.46	>100	>100
21	4	C_2H_5	CH_3	CH_3	66.5–67.5	T–Hx	21	*j*						40.91	5.69	3.83	8.86	18.23	100	<100
22					87.0–87.3	B–Hx	47	$C_{17}H_{22}NO_8PS_3$	41.21	4.48		6.25	19.41	41.51	4.76		5.98	19.46	>100	<100

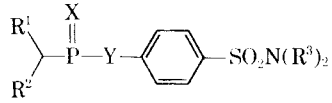
[a] Refers to position of attachment of the sulfamoyl group to the ring. [b] Melting points are uncorrected. [c] Where only a refractive index is given, liquids were purified by column chromatography on activated, acid-washed aluminum oxide. Boiling points refer to molecular distillation and indicate the temperature of the heating jacket of the apparatus. [d] Aa, acetone; Ab, acetonitrile; Ac, dilute acetic acid; B, benzene; Ca, carbon tetrachloride; Ch, chloroform; Ea, ethanol; Et, diethyl ether; Ey, ethyl acetate; Hp, heptane; Hx, hexane; I, 2-propanol; Ma, methanol; My, methylene chloride; Pn, pentane; Pt, petroleum ether; T, toluene; W, water. [e] All compounds were prepared by method A, except **8** (method B-1, in ethanol), and **19** (method C, 3 hr. at reflux in methyl ethyl ketone). [f] Yields refer to analytically pure material; in general, no attempt was made to maximize yields. Recovered sulfonamide reactants are not included in yield calculations. [g] Where isomers of earlier entries are encountered (denoted by footnote in formula column), the found values are recorded. [h] The ED_{50} is the oral dose given each of several mice which kills half the mosquitoes taking blood meals from the animals. The LD_{50}, often a rough approximation, is the oral dose killing half the mice. See ref. 6. [i] Same as **1**. [j] Same as **7**. This compound was prepared from the crude sodium salt of N-*t*-butyl-1-phenol-4-sulfonamide (from propanol), m.p. >300°, which in turn was obtained by following the general method for the intermediates and cooling a solution of the phenol in 2 *N* NaOH. [k] Calculated and found values in S column are for Cl. [l] Same as **5**. [m] At −50°. [n] Same as **11**.

TABLE II: DIALKYL SULFAMOYLPHENYL PHOSPHATES $(R^1O)_2P(O)-O-C_6H_4-SO_2N(R^2)_2$

Compd.	Isomer[a]	R^1	R^2	Method	M.p.[b] or b.p. (mm.), °C., or $n^{25}D$[c]	Recrystn. solvent[d]	Yield,[e] %	Formula	Calcd., % C	H	N	P	S	Found, %[f] C	H	N	P	S	Biological data,[g] mg./kg. ED_{50}	LD_{50}
23	4	CH_3	H	C	88–90	T–Ey	38	$C_8H_{12}NO_6PS$	34.16	4.30	4.98	11.02	11.40	34.02	4.24	4.99	11.20	11.63	0.03	13
24	4	CH_3	CH_3	C	68.5–70	Et–Ch	42	$C_{10}H_{16}NO_6PS$	38.83	5.22	4.53	10.02	10.37	38.99	4.86	4.40	9.57	10.26	0.25	1–10
25	4	CH_3	C_2H_5	B-1[h]	118 (0.001) 1.5408		19	$C_{12}H_{20}NO_6PS$	42.72	5.98	4.15	9.18	9.51	42.70	5.73	4.35	9.24	9.48		
26	3	C_2H_5	H	*i*	79.5–80.5	W[i]	21	*k*						38.43	5.23	4.72	9.31	10.72	>100	75
27	4	C_2H_5	H	C[l]	79.5–81.5	W[i]	38	*k*						38.73	5.07	4.73	9.98		0.03	22
28	4	C_2H_5	CH_3	A	1.4998		60	*m*						43.10	6.58	4.28	9.15	9.58	>10	30

[a] See footnote *a*, Table I. [b] See footnote *b*, Table I. [c] See footnote *c*, Table I. [d] See footnote *d*, Table I. [e] See footnote *f*, Table I. [f] See footnote *g*, Table I. [g] See footnote *h*, Table I. [h] Methyl ethyl ketone solvent. [i] See Experimental. [j] A 1:1 mixture of **76** and **77** had m.p. 55–64°. [k] Same as **24**. [l] Refluxing methyl ethyl ketone solvent for 5 hr. [m] Same as **25**.

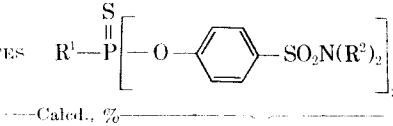
TABLE III: PHOSPHORYLATED *p*-BENZENESULFONAMIDES

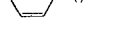


Compd.	R^1	R^2	X	Y	R^3	Method	M.p.[a] or b.p. (mm.), °C., or $n^{25}D$[b]	Recrystn. solvent[c]	Yield,[d] %	Formula	Calcd., % C	H	N	P	S	Found, % C	H	N	P	S	Biological data,[e] mg./kg. ED_{50}	LD_{50}
29	CH_3O	CH_3O	O	SCH_2	H	D	136–138	I	71	$C_9H_{14}NO_6PS_2$	34.72	4.53	4.50	9.95		34.77	4.58	4.34	9.86		>100	>100
30	CH_3O	CH_3O	S	SCH_2	H	D	91–94	B	63	$C_9H_{14}NO_4PS_3$	33.03	4.31	4.28	9.47	29.38	33.63	4.25	4.42	9.99	29.13	>100	>100
31	CH_3O	CH_3O	S	S	H	E	103.5–105	Ch	26	$C_8H_{12}NO_4PS_3$	30.67	3.86	4.47	9.89		30.84	3.69	4.40	10.00		50	>100
32	C_2H_5O	C_2H_5O	S	SCH_2	H	D	81.5–83.5	B	73	$C_{11}H_{18}NO_4PS_3$	37.17	5.10	3.94	8.72	27.06	37.19	5.19	3.98	8.46	26.81	>50	>50
33	C_2H_5O	C_2H_5O	S	S	H	E	1.5899		26	$C_{10}H_{16}NO_4PS_3$	35.17	4.72	4.09	9.08	28.17	34.85	4.77	3.98	9.13	27.93	75	75
34	C_2H_5O	C_2H_5O	S	NH	H	*f*	157–158	W	6	$C_{10}H_{17}N_2O_4PS_2$	37.03	5.28	8.64	9.55	19.77	37.12	5.08	8.94	9.28	19.52	>100	>100
35	C_2H_5	C_2H_5	S	O	CH_3	B-1	91–91.5	Ea	60	$C_{12}H_{20}NO_3PS_2$	44.84	6.27	4.36	9.64	19.95	45.07	6.04	4.35	9.87	20.01	1–10	10–100
36	CH_3NH	CH_3NH	S	O	H	F	99.5–100.5	W	44	$C_3H_{11}N_3O_3PS_2$	32.54	4.78	14.23	10.49		33.01	4.64	14.27	10.02		40	>100
37	CH_3NH	CH_3NH	S	O	CH_3	F	119.5–120.5	Ch–Pt	2[g]	$C_{10}H_{18}N_3O_3PS_2$	37.13	5.61	13.00	9.58	19.83	38.03	5.78	13.15	9.71	20.35	10–100	10–100
38	C_2H_5NH	C_2H_5NH	S	O	CH_3	F	106–107	Et–Ab	1[g]	$C_{12}H_{22}N_3O_3PS_2$	41.01	6.31	11.96	8.82	18.25	41.31	6.26	11.82	8.61	18.54	85	100
39	Cl	Cl	S	O	H	B-2	99.5–100.5	B–Hx	21	$C_6H_6Cl_2NO_3PS_2$	23.54	1.98		10.12		25.17	2.53		9.32[h]			
40	Cl	Cl	S	O	CH_3	B-1	67.5–70	Et–Pn[i]	17	$C_3H_{10}Cl_2NO_3PS_2$	28.75	3.02	4.19	9.27	19.19[j]	28.93	3.14	4.31	9.14	18.94		
41	CH_3O	CH_3S	O	SCH_2	H	D	103–104	My	34	$C_9H_{14}NO_4PS_3$	33.03	4.31	4.28	9.47		32.94	4.36	4.21	9.16		>100	>100
42	CH_3O	C_2H_5O	S	O	CH_3	B-1[k]	52–53.5	Ea–W	46	$C_{11}H_{18}NO_5PS_2$	38.93	5.34	4.13	9.13	18.89	39.20	5.13	4.26	9.33	18.98	8	25–50
43	C_2H_5O	$(CH_3)_2N$	S	O	CH_3	B-1[l]	65–66.5	Et[m]	60	$C_{12}H_{21}N_2O_4PS_2$	40.90	6.01	7.95	8.79	18.20	41.14	6.21	8.05	8.72	18.12	>100	90
44	C_2H_5O	$(CH_3)_2N$	O	O	CH_3	B-1[n]	132–133 (0.002) 1.5085		45	$C_{12}H_{21}N_2O_5PS$	42.85	6.29	8.33	9.21	9.53	40.95	6.24	8.07	8.82	9.24	>100	10–100
45	C_2H_5O	C_6H_5	S	O	CH_3	B-1[o]	160–162 (0.003) 1.5789		52	$C_{16}H_{20}NO_4PS_2$	49.86	5.23	3.63	8.04	16.63	49.91	5.28	3.67	8.12	16.62	100	>100

[a] See footnote *b*, Table I. [b] See footnote *c*, Table I. [c] See footnote *d*, Table I. [d] See footnote *f*, Table I. [e] See footnote *h*, Table I. [f] See Experimental. [g] Prepared from **40** of unknown purity. [h] Compound decomposed during attempted analysis. [i] At −55°. [j] Calcd.: Cl, 21.22. Found: Cl, 21.20. [k] For the preparation of the starting ethyl methyl phosphorochloridothioate see N. N. Mel'nikov, Y. A. Mandelbaum, V. I. Lomakina, and Z. M. Bakanova, *J. Gen. Chem. USSR*, 2577 (1956); "Soviet Research on Organo-phosphorus Compounds, 1949–1956," Consultants Bureau Inc., New York, N. Y., 1960, Part I, p. 288. [l] For the preparation of the starting O-ethyl dimethylphosphoramidochloridothioate see M. I. Kabachnik, N. M. Godovikov, D. M. Paikin, M. P. Shabanova, L. F. Efimova, and N. M. Gamper, *Zh. Obshch. Khim.*, **29,** 2182 (1959); *Chem. Abstr.*, **54,** 10830c (1960). [m] At −75°. [n] For the preparation of the starting O-ethyl dimethylphosphoramidochloridate see H. G. Cook, J. D. Hett, B. C. Saunders, G. C. Stacey, H. G. Watson, I. G. E. Wilding, and S. J. Woodcock, *J. Chem. Soc.*, 2921 (1949). For the preparation of the starting O-ethyl phenylphosphonochloridothioate see M. F. Hersman and L. F. Audrieth, *J. Org. Chem.*, **23,** 1889 (1958).

TABLE IV: POLY(O-*p*-SULFAMOYLPHENYL) PHOSPHOROTHIOATES



Compd.	R^1	R^2	M.p., °C.[a]	Recrystn. solvent[b]	Yield,[c,d] %	Formula	Calcd., % C	H	N	P	S	Found, % C	H	N	P	S	Biological data,[e] mg./kg. ED_{50}	LD_{50}
46	Cl	CH_3	195.5–196	Ch–Et	50	$C_{16}H_{20}ClN_2O_6PS_3$	38.51	4.04	5.62	6.21	19.28	38.71	3.95	5.54	6.40	19.62		
47	C_2H_5O	CH_3	109–110	Ma	53	$C_{18}H_{25}N_2O_7PS_3$	42.50	4.95	5.51	6.09	18.91	43.03	5.07	5.27	5.98	18.98	>100	100–1000
48		H	198.5–200	Ea–W	17	$C_{18}H_{18}N_3O_9PS_4$	37.30	3.13	7.25	5.34		37.40	3.20	7.43	5.23		>100	>100

[a] See footnote *b*, Table I. [b] See footnote *d*, Table I. [c] Compound **46** was prepared by method B-2; **47** and **48** were prepared by method B-1 using as phosphorylating agents **46** and thiophosphoryl chloride, respectively. [d] See footnote *f*, Table I. [e] See footnote *h*, Table I.

TABLE V

1-PHENOL-4-SULFONAMIDES

Compd.	R′	R‴	M.p., °C.[a]	Recrystn. solvent[b]	Yield, %[c]	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Calcd., % S	Found, % C	Found, % H	Found, % N	Found, % S
49	H	CH_3	91.5–92	B–Ey	23	$C_7H_9NO_3S$	44.91	4.85	7.48		44.81	4.85	7.42	
50	H	C_2H_5	105–105.5	T–Ey	48	$C_8H_{11}NO_3S$	47.7	5.48	6.97	15.9	47.6	5.39	6.77	15.7
51	H	C_3H_7-*i*	91–93	Aa[d]	45	$C_9H_{13}NO_3S$	50.3	6.10	6.52	14.9	50.3	5.93	6.55	14.7
52	H	C_4H_9-*n*	79–81	B–Ey	45	$C_{10}H_{15}NO_3S$	52.37	6.59	6.11	13.98	51.80	6.53	5.87	14.14
53	H	C_4H_9-*t*	115–115.5	T–Ey	*e*	$C_{10}H_{15}NO_3S$	52.37	6.59	6.11	13.98	52.17	6.86	6.15	13.88
54	$-(CH_2)_2O(CH_2)_2-$		151–152	W	79	$C_{10}H_{13}NO_4S$	49.3	5.35	5.76	13.2	49.4	5.31	5.81	13.1
55	HO–C₆H₄–SO_2O–	$SO_2NHC_6H_5$-*i*	164–165.5	Ac	3.7[f]	$C_{15}H_{17}NO_6S_2$	48.51	4.62	3.77	18.61	48.50	4.69	3.73	18.22

[a] See footnote *b*, Table I. [b] See footnote *d*, Table I. [c] All compounds were prepared by the general method, except **49** (see Experimental). [d] At −10°. [e] This compound was recovered during chromatographic purification of the corresponding phosphorothioate (Table I, 8). [f] As by-product in preparation of N-isopropyl-1-phenol-4-sulfonamide (see Experimental).

mation of an intermediate 4-benzoyloxybenzenesulfonamide (not isolated) and subsequent hydrolysis of the benzoate linkage. Since some cleavage of the benzoate linkage by the amine was usually observed using this method, later work emphasized the use of excess amine to affect the cleavage quantitatively, thereby eliminating the hydrolysis step; yields, in general, were higher by this method. Data in Table V are for the two-step procedure, except for **49**.

During the course of one large-scale preparation of **51** by the two-step procedure, a small amount of *p*-(isopropylsulfamoyl)phenyl 1-phenol-4-sulfonate (**55**) was isolated. Phosphorylation of this material gave the sulfonate ester (Table I, **22**).

The procedures for determining systemic insecticidal activity (ED_{50}) and mouse toxicity (LD_{50}) by means of the mouse–mosquito test have been reported.[6] In general, the phosphates I (X and Y = O; R and R′ = alkoxy) and phosphorothioates I (X = S; Y = O; R and R′ = alkoxy) are the insecticidally most active members of the series, the phosphates in most cases being more active but exhibiting decidedly higher mammalian toxicity. The O,O-dimethyl esters are more active and have more attractive (higher) LD_{50}/ED_{50} ratios than the corresponding O,O-diethyl homologs. Placement of the sulfamoyl group *ortho* or *meta* to the phenolic oxygen results in a marked loss of insecticidal activity with respect to *para* substitution. Lower alkyl substituents on the sulfonamide group nitrogen atom decrease systemic insecticidal activity somewhat with respect to the unsubstituted compounds, but toxicity decreases markedly. Substitution with acyl groups gives a high degree of activity, but aryl, higher alkyl, or heterocyclic substituents on the nitrogen result in loss of activity.

Experimental[7]

Phosphorylated Benzenesulfonamides. Method A. O,O-Dimethyl O-*p*-(Dimethylsulfamoyl)phenyl Phosphorothioate (14).—O,O-Dimethyl phosphorochloridothioate (4.01 g., 0.025 mole) was added dropwise to a solution of N,N-dimethyl-1-phenol-4-sulfonamide (5.03 g., 0.025 mole) in 50 ml. of 0.5 *N* aqueous NaOH. During the chloridothioate addition, 25 ml. of 1.0 *N* aqueous NaOH solution was added dropwise to the reaction mixture. After stirring 3 hr., the mixture was extracted with ether, the ethereal extracts were dried ($MgSO_4$), and the solvent was evaporated to give 3.8 g. (47%) of white solids, m.p. 52.5–53.0°. Two recrystallizations from toluene–hexane gave 2.2 g. (27%) of white crystals, m.p. 52.5–53.5°. Acidification of the reaction mixture aqueous layer gave 2.5 g. (50% recovery) of N,N-dimethyl-1-phenol-4-sulfonamide, m.p. 95–96°. A similar preparation, on a 0.44 *M* scale, gave a 41% yield of product with m.p. 52.0–53.0° (toluene–hexane) and a 38% recovery of starting phenolsulfonamide, m.p. 94–95°.

O,O-Dimethyl O-*p*-(Methylsulfamoyl)phenyl Phosphorothioate (4).—A mixture of N-methyl-1-phenol-4-sulfonamide (21.3 g., 0.114 mole), O,O-dimethyl phosphorochloridothioate (18.3 g., 0.114 mole), and 230 ml. of 0.5 *N* NaOH solution (0.115 mole) was heated to 40° and the pH was adjusted to 8–10 by addition of 1.0 *N* NaOH solution. Base consumption ceased after *ca.* 1

(6) R. Hewitt, A. Brebbia, and E. Waletzky, *J. Econ. Entomol.*, **51**, 126 (1958).

(7) Melting points were taken on a Fisher-Johns block or in a Thomas–Hoover capillary apparatus and are uncorrected. Boiling points refer to molecular distillation and indicate the temperature of the heating jacket of the apparatus. Infrared absorption spectra were taken on all compounds prepared, using a Perkin-Elmer Infracord (Model 137) spectrophotometer; all spectra were consistent with the postulated structures. The assistance of Mr. N. B. Colthup and Mr. R. S. Wayne in interpreting these spectra is acknowledged.

hr. The separated dense oil was extracted with ether, the ethereal extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure to yield 23.2 g. (66%) of viscous liquid. Dissolution in toluene and precipitation with hexane, at −24°, gave 21.7 g. (61%) of white crystals, m.p. 36.0–38.0°.

O-*p*-(Acetylsulfamoyl)phenyl O,O-Dimethyl Phosphorothioate (10).—N-Acetyl-1-phenol-4-sulfonamide (10.8 g., 0.05 mole) was suspended in 100 ml. of water and the pH was adjusted to read 11.0 (25°) with 1.0 *N* NaOH solution. O,O-Dimethyl phosphorochloridothioate (12.0 g., 0.075 mole, 50% excess) was added in one portion and the vigorously stirred mixture was maintained at pH 11.0 by addition of the 1.0 *N* base solution. Base consumption ceased after *ca.* 1 hr. The homogeneous solution was acidified with concentrated HCl, and the white crystal crop was collected and dried; m.p. 142–144°, yield 11.9 g. (70%). Recrystallization from 200 ml. of toluene (−15°) gave 11.5 g. (68%), m.p. 142–144°.

Method B. O-*p*-(Dimethylsulfamoyl)phenyl Diethylphosphinothioate (35).—To a refluxing suspension of the sodium salt of N,N-dimethyl-1-phenol-4-sulfonamide[8] (11.2 g., 0.05 mole) in 100 ml. of acetonitrile was added diethyl phosphinothioyl bromide[9] (10.0 g., 0.05 mole) over a 5-min. period. The reaction mixture was heated at reflux for 5 min. and filtered, and the solvent was removed from the filtrate *in vacuo*, yielding 15.7 g. of tan solids. Recrystallization from 60 ml. of CCl_4 gave a tan powdery solid, m.p. 90–91°; a second recrystallization from ethanol gave 9.7 g. (60%) of white crystals, m.p. 91.0–91.5°.

O-*p*-Sulfamoylphenyl Phosphorodichloridothioate (39).—The crude sodium derivative of 1-phenol-4-sulfonamide[10] was prepared by mixing equimolar quantities of 1-phenol-4-sulfonamide and sodium ethoxide in ethanol solvent, removing the ethanol *via* the benzene–ethanol azeotrope, and drying the separated solids to constant weight. A mixture of 9.8 g. (0.05 mole) of this material, 50 g. (excess) of thiophosphoryl chloride, and 5 drops of PCl_3 was heated gently on the steam bath. At 70° a strong exotherm set in and was controlled with an ice bath. The mixture was reheated to 95° for 20 min., cooled, and evaporated to dryness under reduced pressure to yield 6.2 g. (40%) of white solids. Recrystallization from benzene–hexane gave 3.2 g. (21%) of white crystals with m.p. 99.5–100.5° (also recrystallizable from thiophosphoryl chloride). The material is unstable at room temperature; a satisfactory elemental analysis could not be obtained. A sample of the material was derivatized to give **36**.

Method C. Dimethyl *p*-(Dimethylsulfamoyl)phenyl Phosphate (24).—A mixture of dimethyl phosphorochloridate (8.7 g., 0.06 mole, 20% excess), N,N-dimethyl-1-phenol-4-sulfonamide (10.1 g., 0.05 mole), and Na_2CO_3 (5.3 g., 0.05 mole) in 100 ml. of acetone was heated at reflux for 4 hr., cooled to 25°, and filtered. The solvent was removed from the filtrate *in vacuo*, and the residual liquid was held at 55° (1.5 mm.) for 30 min. to remove unreacted dimethyl phosphorochloridate to give 15.0 g. (97%) of colorless liquid. This liquid was dissolved in 50 ml. of chloroform, the solution was washed with three 10-ml. portions of 10% K_2CO_3 solution and 10 ml. of water and dried ($MgSO_4$). Removal of the solvent *in vacuo* yielded 14.2 g. (92%) of cloudy, viscous, colorless liquid. The liquid was placed on a 2.5 × 25 cm. column of activated, acid-washed aluminum oxide (Woelm), in CCl_4. Elution with 200 ml. of CCl_4 removed 0.2 g. of material from the column. Elution with 400 ml. of benzene removed 7.0 g., $n^{25}D$ 1.5109; 400 ml. of $CHCl_3$ removed 3.1 g., $n^{25}D$ 1.5108. A final elution with 400 ml. of acetone did not remove any material from the column. The two fractions of product which were collected in benzene and $CHCl_3$ effluents (10.1 g., 65%) could not be crystallized and gave analytical values within 0.3% for C, H, N, P, and S. Upon prolonged storage (*ca.* 11 months at 25°), the fractions crystallized, m.p. 63–66°. Two recrystallizations from chloroform ether gave a 65% recovery (42% yield) of white crystals, m.p. 68.5–70.0°.

Method D. O,S-Dimethyl S-*p*-Sulfamoylbenzyl Phosphorodithioate (41).—Potassium O,S-dimethyl phosphorodithioate[11] (9.8 g., 0.05 mole) and 4-bromomethylbenzenesulfonamide (12.5 g., 0.05 mole) were dissolved in 100 ml. of acetone, and the solution was stirred for 1.25 hr. The temperature rose to 31° as a granular, white precipitate formed. Filtration gave 5.6 g. of solids (94% yield of KBr). The solvent was removed from the filtrate, *in vacuo*, to give 18.6 g. of sirup which yielded crystals (m.p. 99–100°) from $CHCl_3$. Recrystallization from chloroform, then methylene chloride, gave 5.5 g. (34%) of white crystals, m.p. 103.0–104.0° (cap.).

Method E. O,O-Dimethyl S-*p*-Sulfamoylphenyl Phosphorodithioate (31).—The procedure used for the preparation of the sulfanilamide diazonium salt was patterned after the method of Clifford and Lichty[12] for anilinium salts. Mel'nikov, *et al.*,[13] have reported the reaction of O,O-dialkyl phosphorodithioates with aryl diazonium salts. A solution of sulfanilamide (8.6 g., 0.05 mole) and 30 ml. of 10% HCl (8.34 ml., 0.1 mole of concentrated acid) was diluted to 75 ml. with water and cooled in an ice–methanol bath. A solution of $NaNO_2$ (3.52 g., 0.051 mole, 2% excess) in 15 ml. of water was added slowly to the 0–5° sulfanilamide solution. Air was bubbled through the mixture until a negative test for nitrite was obtained with starch–iodide paper. The mixture was stirred at 0°, and potassium O,O-dimethyl phosphorodithioate (9.82 g., 0.05 mole) and powdered copper (0.05 g.) were added. The stirred mixture was allowed to warm to 25° and finally heated at 50° for 3 hr. Extraction with ether, treatment of the ethereal solution with activated carbon, drying ($MgSO_4$), and evaporation of solvent gave 11.5 g. (74%) of viscous, brown liquid. This liquid was placed on a 2.5 × 25 cm. column of activated, acid-washed aluminum oxide (Woelm) in benzene, and elution carried out successively with benzene (500 ml.), $CHCl_3$ (1000 ml.), and ether (300 ml.). The chloroform and ether effluents yielded a total of 5.9 g. of solids, m.p. 103.5–104.5°. Recrystallization from chloroform gave 4.0 g. (26%) of white needles, m.p. 103.5–105.0°.

Method F. O-*p*-Sulfamoylphenyl N,N′-Dimethylphosphorodiamidothioate (36).—To a mixture of O-*p*-sulfamoylphenyl phosphorodichloridothioate (3.1 g., 0.01 mole) in 50 ml. of benzene was added dropwise a solution of methylamine (1.2 g., 0.04 mole) in 25 ml. of benzene, the temperature of the strongly exothermic reaction being maintained at 25°. After addition, the mixture was heated to 60° for 5 min., cooled to 25°, and filtered. The solids were partitioned in 100 ml. of ether and 20 ml. of water, the ethereal solution was washed with two 10-ml. portions of water and dried ($MgSO_4$), and the solvent was evaporated to yield 2.5 g. (85%) of white crystals, m.p. 97–99°. Two recrystallizations from water gave 1.3 g. (44%), m.p. 99.5–100.5°.

Diethyl *m*-Sulfamoylphenyl Phosphate (26).—To a solution of 1-phenol-3-sulfonamide (7.8 g., 0.045 mole) and pentamethylguanidine (5.8 g., 0.045 mole) in 50 ml. of ether was added, dropwise, diethyl phosphorochloridate (7.8 g. 0.045 mole), the mildly exothermic reaction being maintained at 25°. The mixture was heated at reflux for 6 hr., and the ether was decanted from a viscous residual liquid. This liquid was dissolved in $CHCl_3$, the chloroform solution was washed with three 10-ml. portions of water, treated with activated carbon, and dried ($MgSO_4$), and the solvent was evaporated to give 5.0 g. (35%) of tan solids. Two recrystallizations from water gave 2.9 g. (21%) of tan crystals, m.p. 79.5–80.5°.

O,O-Diethyl *p*-Sulfamoylphenylphosphoroamidothioate (34).—O,O-Diethyl phosphorochloridite (7.8 g., 0.05 mole) was added dropwise to a solution of sulfanilamide (8.6 g., 0.05 mole) and triethylamine (5.0 g., 0.05 mole) in 100 ml. of tetrahydrofuran, the exothermic reaction being maintained at 25°. After stirring at 25° for 2 hr., the amine hydrochloride (6.8 g., 100%) was filtered off, and sulfur (1.6 g., 0.05 mole) was slowly added to the filtrate, the exothermic reaction being maintained at 25°. The solution was heated at reflux for 15 min., cooled to 25°, and filtered, and the solvent was evaporated from the filtrate to yield a pale yellow slurry. The slurry was dissolved in acetone, unreacted sulfur (0.3 g., 19% yield) was filtered off, and unreacted sulfanilamide was recovered by flooding the concentrated filtrate with benzene. The solvents were removed from the filtrate to yield 6.1 g. (38%) of yellow, viscous liquid which slowly solidified (6 days at 25°). Three recrystallizations from chloroform and one from water gave 1.0 g. (6%) of tan crystals, m.p. 157.0–

(8) E. L. Eliel and K. W. Nelson, *J. Org. Chem.*, **20**, 1657 (1955).

(9) W. Kuchen and H. Buchwald, *Angew. Chem.*, **71**, 162 (1959), report only b.p. 112.5° (12.5 mm.); we find b.p. 50–51° (0.25 mm.), $n^{25}D$ 1.5679. *Anal.* Calcd. for $C_4H_{10}BrPS$: C, 23.89; H, 5.01; Br, 39.75; P, 15.41; S, 15.94. Found: C, 24.11; H, 5.23; Br, 39.87; P, 15.39; S, 16.02.

(10) W. O. Kermack, W. T. Spragg, and W. Tebrich, *J. Chem. Soc.*, 608 (1939).

(11) G. Schrader, German Patent 1,141,634 (1962).

(12) A. M. Clifford and J. G. Lichty, *J. Am. Chem. Soc.*, **54**, 1163 (1932).

(13) N. N. Mel'nikov, A. F. Grapov, and K. D. Shvetsova-Shilovskaya, *Zh. Obshch. Khim.*, **27**, 1905 (1957); *Chem. Abstr.*, **52**, 4533*c* (1958).

158.0°. The chloroform recrystallizations gave poor recovery and did not appreciably improve the melting point.

1-Phenol-4-sulfonamides. General Method. N-Ethyl-1-phenol-4-sulfonamide (50).—To 29.7 g. (0.1 mole) of the benzoate of 1-phenol-4-sulfonyl chloride[14] in 100 ml. of 3 *N* NaOH cooled in an ice bath was added dropwise 4.5 g. (0.1 mole) of ethylamine. The mixture was stirred in the ice bath for 1.25 hr., heated on the steam bath for 1.25 hr., cooled to 25°, and acidified with concentrated HCl. The mixture was extracted with a total of 80 ml. of ether, the organic solution was washed with three 20-ml. portions of 20% K_2CO_3, then 20 ml. of water, and dried ($MgSO_4$), and the solvent was removed under reduced pressure to give 18.8 g. of viscous, brown liquid. Recovered benzoic acid from the aqueous wash liquids amounted to only a 71% yield, indicating some aminolysis of the ester linkage. The crude product was dissolved in 25 ml. of 3 *N* NaOH, and the solution was extracted with ether, yielding 2.2 g. of N-ethylbenzamide in the ether layer. The aqueous layer was acidified and extracted with ether. Evaporation of the solvent gave 14.5 g. of light brown liquid which slowly crystallized, m.p. 98°. Recrystallization from toluene–ethyl acetate gave 9.7 g. (48%) of white crystals with m.p. 105.0–106.5°.

Use of Excess Amine. N-Methyl-1-phenol-4-sulfonamide (49).—To approximately 75 ml. of methylamine at −75° was added slowly and in small portions the benzoate of 1-phenol-4-sulfonyl chloride[14] (29.7 g., 0.1 mole), followed by 100 ml. of ether. Stirring was continued at −75° for 0.5 hr., then at −1° (reflux) for 2.5 hr. Solvent and excess amine were distilled on the steam bath, 100 ml. of water was added to the residue, and the mixture was acidified with concentrated HCl and extracted with ether. The ethereal solution was washed with two 15-ml. portions of water and dried ($MgSO_4$), and the solvent was evaporated to give 27.9 g. of viscous, brown liquid. Addition of 3 *N* NaOH to the liquid precipitated crystals of N-methylbenzamide, m.p. 78.5–79.5° (8.8 g., 65%). Reacidification of the basic filtrate gave a paste, which was dried on a clay plate to give 5.2 g. of white crystals with m.p. 80–81.5°. Recrystallization from benzene–ethyl acetate gave 4.3 g. (23%) of product with m.p. 91.5–92.0°. This material is reported[15] to have m.p. 81–82°.

***p*-(Isopropylsulfamoyl)phenyl 1-Phenol-4-sulfonate (55).**—Isopropylamine (82.9 g., 1.4 moles) was added over a 5-min. period to a stirred slurry of the benzoate of 1-phenol-4-sulfonyl chloride[14] (416 g., 1.4 moles) in 1.4 l. of 3 *N* NaOH at 17°. The temperature was allowed to rise to 40° during 30 min. and maintained at 35–40° during an additional 30 min. The mixture was heated on the steam bath for 45 min., treated twice with activated carbon, and concentrated to two-thirds volume. The mixture was heated to 40°, sufficient water was added to effect homogeneous solution, and the solution was cooled to 10°. The crude sodium derivative of N-isopropyl-1-phenol-4-sulfonamide was filtered off, and the filtrate was acidified with concentrated HCl. The resulting precipitate was taken up in 300 ml. of ether, the ethereal solution was washed with 800 ml. of 20% $KHCO_3$, then with two 100-ml. portions of bicarbonate solution and 100 ml. of water, and the solvent was removed under reduced pressure. The solids were reprecipitated from 10% NaOH with HCl and recrystallized once from aqueous ethanol and three times from 6 *N* acetic acid to give 9.7 g. (3.7%) of white crystals with m.p. 164–165.5°.

Acknowledgment.—We wish to thank Dr. G. Rohrbacher, of these laboratories, and Dr. R. Hewitt, of Lederle Laboratories, for the determination of the biological data.

(14) (a) S. Magnusson, J. E. Christian, and G. L. Jenkins, *J. Am. Pharm. Assoc., Sci. Ed.*, **36**, 257 (1947); (b) M. Schreinemakers, *Rec. trav. chim.*, **16**, 422 (1897).

(15) W. Steinkopf, *J. prakt. Chem.*, [2] **117**, 58 (1927).

Notes

Spiro-3-oxiranyl-5α-androstan-17β-ols

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Received November 21, 1964

The publication of Wolff, Ho, and Kwok[1] describing the spiro-3β-oxiranyl formation from steroid 3-ketones of the allo series with dimethylsulfoxonium methylide prompts us to record our own results in this area.

After the introduction of the methylenation method by Corey and Chaykovsky[2] we have methylenated 5α-androstan-17β-ol-3-one (I) and in agreement with Wolff and co-workers[1] a spiro-3-oxiranyl-5α-androstan-17β-ol, m.p. 171–173° (uncor.), $[\alpha]_D$ +1.93° (*c* 0.94, $CHCl_3$), was obtained. These authors assume that the 3β-oxiranyl compound (II) with an equatorial epoxy oxygen is formed by attack of the reagent from the back side of the molecule. However, according to our results, the 3α-oxiran (III) is formed with sulfoxonium methylide from I. Our assignment is based on the lithium aluminum hydride reduction of III resulting in the formation of the 3β-methyl-5α-androstane-3α 17β-diol (IV).[3] On the other hand, we have obtained the 3β-oxiran (II), m.p. 190.5–191° (uncor.), $[\alpha]^{26}_D$ + 28.8° (*c* 0.90, $CHCl_3$), from the 3-cyanohydrin *via* trimethyl(3β,17β-dihydroxy-5α-androstan-3α-ylmethyl) ammonium iodide (V) by pyrolysis of the free base. The lithium aluminum hydride reduction of II afforded 3α-methyl-5α-androstane-3β,17β-diol (VI).[3] Oxidation of the diols IV and VI led to the 17-ketones VII and VIII[3a] which on acetylation gave the corresponding 3-acetates (IX and X).

As expected, all 3β-oxygenated compounds possessed higher dipole moments[4] than their 3α-epimers (see Table I). The fact that the 3α-acetate IX showed complex acetoxy bands in the 8-μ region of the infrared whereas the 3β-acetate X had a single band[5] confirms our assignment of the configuration at C-3. Neither epimeric spiro-3-oxirane showed anabolic or androgenic activity after subcutaneous application in rats in the Hershberg assay.

TABLE I

Compd.	μ calcd.	μ found
II	2.50	2.61 dioxane
III	2.33	2.24 dioxane
VII	3.32	3.55 benzene
		3.73 dioxane
VIII	2.26	2.75 dioxane

(1) M. E. Wolff, W. Ho, and R. Kwok, *J. Med. Chem.*, **7**, 577 (1964).

(2) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **84**, 867 (1962).

(3) (a) J. Kathol, Schering AG, German Patent 881,945 (April 7, 1951); *Chem. Zentr.*, 10329 (1955); (b) B. Pelc, *Collection Czech. Chem. Commun.*, **25**, 1624 (1960).

(4) For a description of the calculation and measurement of dipole moments, see W. Neudert and H. Röpke, "Steroid Atlas," Springer-Verlag, Berlin, 1965.

(5) R. N. Jones, P. Humphries, F. Herling, and K. Dobriner, *J. Am. Chem. Soc.*, **73**, 3215 (1951); H. Rosenkrantz and P. Skogstrom, *ibid.* **77**, 2237 (1955).