Table VI
2-Chloroethyl- and Bis(2-chloroethyl)amides of Amino Acids

$$R-CH(NH_2)CON(X)$$

R (amino acid)	X	Yield, %	M.p., °C.	ν_{max}, cm.$^{-1}$	Formula	Calcd., % C	H	N	Cl	Found, % C	H	N	Cl
H (Gly)	$NHCH_2CH_2Cl$	77	165–166	1665	$C_4H_9ClN_2O\cdot HCl$	27.76	5.82	16.19	40.98	27.9	5.8	15.9	40.9
CH_3 (DL-Ala)	$NHCH_2CH_2Cl$	66	141–143	1660	$C_5H_{11}ClN_2O\cdot HCl$	32.10	6.47	14.97	37.90	32.2	6.4	14.9	38.1
CH_3 (L-Ala)	$NHCH_2CH_2Cl$	92	179–180	1660	$C_5H_{11}ClN_2O\cdot HCl$[a]	32.10	6.47	14.97	37.90	31.9	6.6	15.0	37.9
$CH_2C_6H_5$ (DL-Phe)	$NHCH_2CH_2Cl$	70	153–154	1665	$C_{11}H_{15}ClN_2O\cdot HCl$	50.20	6.13	10.65	26.95	50.1	6.2	10.6	26.9
$CH_2CH(CH_3)_2$ (DL-Leu)	$NHCH_2CH_2Cl$	81	136–138	...	$C_8H_{17}ClN_2O\cdot HCl$	41.93	7.92	12.23	30.95	42.2	7.9	12.2	31.2
$CH_2CH_2CO_2H$ (L-γ-Glu)	$NHCH_2CH_2Cl$	65	104–105	1670	$C_7H_{13}ClN_2O_3$[b]	40.28	6.28	13.43	16.98	40.3	6.4	13.4	17.6
CH_2CONH_2 (DL-Asp-NH_2)	$NHCH_2CH_2Cl$	30	154–156	1676, 1657	$C_6H_{12}ClN_3O_2\cdot C_2H_2O_4$	33.87	4.98	14.81	12.50	34.0	5.0	14.6	12.3
CH_2CONH_2 (DL-Asp-NH_2)	$NHCH_2CH_2Cl$	..	155–157	...	$C_6H_{12}ClN_3O_2\cdot C_6H_3N_3O_7$	34.09	3.58	19.88	8.38	34.1	3.7	19.8	8.2
H (Gly)	$N(CH_2CH_2Cl)_2$	86	163–165	1660	$C_6H_{12}Cl_2N_2O\cdot HCl$	30.59	5.56	11.90	45.14	30.5	5.5	11.7	45.0
H (Gly)	$N(CH_2CH_2Cl)_2$	46	114–115	1660	$C_6H_{12}Cl_2N_2O\cdot C_2H_2O_4\cdot H_2O$	31.90	5.25	9.12	23.09	31.5	4.9	9.1	23.0
CH_3 (DL-Ala)	$N(CH_2CH_2Cl)_2$	72	116–118	1665	$C_7H_{14}Cl_2N_2O\cdot C_2H_2O_4$	35.64	5.28	9.24	23.43	35.6	5.3	9.1	23.1
$CH_2C_6H_5$ (DL-Phe)	$N(CH_2CH_2Cl)_2$	85	158–161	1660	$C_{13}H_{18}Cl_2N_2O\cdot HCl$	45.41	6.17	8.15	30.91	45.4	6.2	8.1	31.0
$CH_2C_6H_5$ (DL-Phe)	$N(CH_2CH_2Cl)_2$	53	114–116	1660	$C_{13}H_{18}Cl_2N_2O\cdot C_2H_2O_4$	47.49	5.28	7.38	18.73	47.5	5.4	7.3	19.1
$CHCH_2(CH_3)_2$ (DL-Leu)	$N(CH_2CH_2Cl)_2$	80	180–182	1660	$C_{10}H_{20}Cl_2N_2O\cdot HCl$	41.18	7.26	9.61	36.47	41.2	7.2	9.8	36.7

[a] $[\alpha]^{25}D$ +5.2° (*c* 3.49, water). [b] $[\alpha]^{25}D$ +22.8° (*c* 1.23, water).

N-Carbobenzoxy-DL-phenylalanine 2-Chloroethylamide (Method A).—To 0.6 g. of N-carbobenzoxy-DL-phenylalanine 2-hydroxyethylamide in $CHCl_3$ (10 ml.) was added dropwise, 0.6 ml. of thionyl chloride at ice-bath temperature, while stirring magnetically. The ice bath was then removed, a drop of pyridine was added, and stirring was continued at room temperature for 1 hr. and at 40–45° for 2 hr. The solvent and excess thionyl chloride were removed *in vacuo* and the residual solid (0.55 g.) was crystallized from benzene–methylcyclohexane: m.p. 125–127°.

N-Carbobenzoxy-DL-asparagine 2-Chloroethylamide (Method C).—N-Carbobenzoxy-DL-asparagine cyanomethyl ester (0.77 g., 0.0025 mole) was dissolved in 30 ml. of ethyl acetate. To this solution cooled in ice, the freshly liberated base 2-chloroethylamine was added. (The latter reactant was prepared by neutralizing 2-chloroethylamine hydrochloride (0.45 g., 0.004 mole) to pH around 9 with 2 *N* NaOH in an ice bath, subsequent extraction into ethyl acetate, and drying (Na_2SO_4) while in an ice bath.) The reaction mixture was stirred at the ice-bath temperature for 2 hr. and at room temperature overnight. The white solid which separated was collected on a filter, washed with a little cold ethyl acetate, and crystallized from a mixture of ethyl acetate–ethanol; yield 0.4 g. (50%), m.p. 192–194°.

N-Carbobenzoxyamino Acid Bis(2-chloroethyl)- and 2-Chloroethylamides (Method B).—To a solution of 1 mole of N-carbobenzoxyamino acid in $CHCl_3$ or methylene chloride and 2–3 moles of bis(2-chloroethyl)amine or 2-chloroethylamine (freshly prepared from the equivalent amount of their respective hydrochlorides as described in the previous experiment excepting that the base was extracted into an ice-cold $CHCl_3$ solution instead of ethyl acetate) was added 1.0 mole of N,N′-dicyclohexylcarbodiimide. The mixture was stirred at ice-bath temperature for 1–2 hr. and left around 10° overnight. The precipitated dicyclohexylurea was filtered. The filtrate was washed successively with 1 *N* HCl, water, saturated $NaHCO_3$, and water then dried (Na_2SO_4). The residue obtained after evaporation of the solvent under reduced pressure at room temperature was taken up in ethyl acetate and the insoluble material was filtered. The ethyl acetate solution, on evaporation under reduced pressure at ordinary temperature, left a residue which was crystallized to produce analytically pure product.

Sulfonanilides. I. Monoalkyl- and Arylsulfonamidophenethanolamines[1,2]

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Incorporation of the alkyl- or arylsulfonamido moiety into the benzene ring of phenethanolamines leads to a series of compounds, members of which have significant biological actions. The chemical rationale for the use of this substituent, on the basis of its acidity and spacial geometry, is discussed. Prominent pharmacologic properties of this series of monosulfonamidophenethanolamines are β-adrenergic stimulation and blockade and α-adrenergic stimulation. Highly potent and specific β-adrenergic blocking agents were obtained with no demonstrable intrinsic β-mimetic action. The synthesis of the sulfonamidophenethanolamines is reported and the configuration of some *erythro* and *threo* racemates was confirmed by examination of their n.m.r. spectra.

Elucidation of the structure of the adrenal medullary hormones, epinephrine and norepinephrine,[3] provided the impetus for extensive molecular modifications of these catecholamines.[4] Although the benzenoid hydroxyl group of the catecholamine has been replaced with a variety of substituents including chlorine,[5a] fluorine,[5b] iodine,[5c] alkyl,[5d] nitro,[5e] amino,[5f] and alkoxy

(1) For preliminary reports of this work see A. A. Larsen and P. M. Lish, *Nature*, **203**, 1283 (1964).

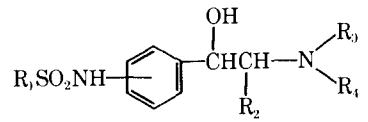
(2) Presented in part at the Division of Medicinal Chemistry, 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1964, Abstracts of Papers, p. 3M.

(3) F. Stolz, *Ber.*, **37**, 4149 (1904); H. A. Jowett, *J. Chem. Soc.*, **85**, 192 (1904).

(4) A. M. Lands, First Symposium on Chemical–Biological Correlation, National Academy of Sciences-National Research Council, 1951, Publication 206, p. 73, provides a 50-year summary and review emphasizing the effects of variation in chemical structure on sympathomimetic amine actions.

(5) (a) J. Mills, U. S. Patent 2,938,921 (May 31, 1960); B. Levy and R. P. Ahlquist, *J. Pharmacol. Exptl. Therap.*, **130**, 334 (1960); (b) L. Villa and E. Grana, *Farmaco* (Pavia), *Sci. Ed.*, **18**, 871 (1963); (c) J. Klepping, R. Michael, H. Tron-Loisel, and R. Trughot, *Compt. Rend. Soc. Biol.*, **154**, 2001 (1960); (d) H. C. Corrodi, H. Persson, A. Carlsson, and J. Roberts, *J. Med. Chem.*, **6**, 751 (1963); (e) U. M. Teotino, L. P. Fritz, G. Steis, and D. Della Bella, *Farmaco* (Pavia), *Sci. Ed.*, **17**, 252 (1961); (f) A. M. Lands, *J. Pharmacol. Exptl. Therap.*, **104**, 474 (1952); U. M. Teotino, L. P. Fritz, G. Steis, and D. Della Bella, *J. Pharm. Pharmacol.*, **15**, 26 (1963); (g) A. M. Hjort, L. O. Randall, and E. J. DeBeer, *J. Pharmacol. Exptl. Therap.*, **92**, 283 (1948); R. Baltzly and J. S. Buck, *J. Am. Chem. Soc.*, **62**, 164 (1940).

TABLE I: SULFONAMIDOPHENETHANOLAMINES

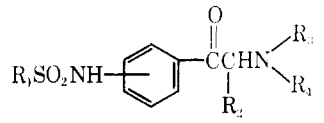


Compd. No.	R_1	R_2	NR_3R_4	Form	Procedure[a]	M.p., °C.	Yield, % (pure)	Crystn. solvent[b]	Formula	% calcd. C	% calcd. H	% calcd. Cl	% found C	% found H	% found Cl
	ortho[c]														
1	CH_3	H	NH_2	HCl	6	186.5–188	66	A–B	$C_9H_{15}ClN_2O_3S$	40.52	5.67	13.29	40.80	5.64	13.27
2	CH_3	H	$NHCH(CH_3)_2$	HCl	*d*	224.5–225.5[e]	67	A–C	$C_{12}H_{21}ClN_2O_3S$	46.67	6.85	11.48	46.36	6.72	11.53
	meta[c]														
3	CH_3	H	NH_2	HCl	5	160–161.5	37	A–B	$C_9H_{15}ClN_2O_3S$	40.52	5.67	13.29	40.63	5.53	12.99
4	n-C_4H_9	H	NH_2	Base	5	121–122.5	42	B–D	$C_{12}H_{20}N_2O_3S$	52.92	7.40	10.29[f]	52.74	7.39	10.21[f]
5	p-$CH_3C_6H_4$	H	NH_2	Base	6	148–152	31	E	$C_{15}H_{18}N_2O_3S$	58.80	5.92	10.46[g]	58.53	6.18	10.58[g]
6	CH_3	H	$NHCH_3$	CH_3SO_3H	5	207–209	75	A	$C_{11}H_{20}N_2O_6S_2$	38.81	5.92	18.84[g]	39.08	5.92	18.60[g]
7	C_2H_5	H	$NHCH_3$	HCl	6	186.5–188.5	49	A–B	$C_{11}H_{19}ClN_2O_3S$	44.81	6.50	12.03	45.00	6.75	11.96
8	p-$CH_3C_6H_4$	H	$NHCH_3$	p-$CH_3C_6H_4SO_3H$	5	157–159	61	E	$C_{23}H_{28}N_2O_6S_2$	56.08	5.73	13.02[g]	56.23	5.63	13.08[g]
9	CH_3	H	NHC_2H_5	CH_3SO_3H	5	132.5–134.5	83	D	$C_{12}H_{22}N_2O_6S_2$	40.66	6.26	18.09[g]	40.95	6.41	17.80[g]
10	CH_3	H	$NHCH_2CH_2C_6H_5$	Base	5	136.5–139.5	53	E	$C_{17}H_{22}N_2O_3S$	61.05	6.63	9.59[g]	60.96	6.92	9.60[g]
11	p-$CH_3C_6H_4$	H	$NHCH_2CH_2C_6H_5$	HCl	5	164–167	68	E	$C_{23}H_{27}ClN_2O_3S$[h]	61.80	6.09	7.93	61.20	6.10	8.08
12	CH_3	H	$NHCH(CH_3)_2$	CH_3SO_3H	5	146–148	29	A–B	$C_{13}H_{24}N_2O_6S_2$	42.37	6.57	17.40[g]	42.56	6.54	17.33[g]
13	n-C_4H_9	H	$NHCH(CH_3)_2$	CH_3CO_2H	*i*	132.5–133.5	61	E	$C_{17}H_{30}N_2O_3S$	54.52	8.08	7.48[f]	54.82	8.31	7.51[f]
14	p-$CH_3C_6H_4$	H	$NHCH(CH_3)_2$	HCl	6	159–161	69	E	$C_{18}H_{25}ClN_2O_3S$	56.16	6.55	9.21	55.88	6.83	9.23
15	CH_3	H	$NHCH(CH_3)CH_2OC_6H_5$	Base	5	158.5–160.5	27	F	$C_{18}H_{24}N_2O_3S$	59.32	6.64	7.69[f]	59.32	6.77	7.56[f]
16	CH_3	CH_3	$NHCH_3$	HCl	5	192.5–194	26	E	$C_{11}H_{19}ClN_2O_3S$	44.81	6.50	12.03	45.00	6.36	12.01
	para[c]														
17	CH_3	H	NH_2	HCl	5	188–189.5[e]	30	A–B	$C_9H_{15}ClN_2O_3S$	...	10.50[f]	13.29	...	10.16[f]	13.30
18	p-$CH_3C_6H_4$	H	NH_2	p-$CH_3C_6H_4SO_3H$	6	178–179.5[e]	56	C–E	$C_{22}H_{26}N_2O_6S_2$	55.21	5.48	13.40[g]	55.49	5.57	13.36[g]
19	CH_3	H	$NHCH_3$	HCl	5	185–186.5	71	A	$C_{10}H_{17}ClN_2O_3S$	42.77	6.10	12.63	42.90	6.09	12.51
20	p-$CH_3C_6H_4$	H	$NHCH_3$	HCl	5	215.5–217[e]	31	D	$C_{16}H_{21}ClN_2O_3S$	53.84	5.93	9.94	54.11	6.02	9.84
21	CH_3	H	$NHCH_2C_6H_5$	HCl	5	202.5–203.5[e]	55	A	$C_{16}H_{21}ClN_2O_3S$	53.84	5.93	9.94	54.09	6.02	9.84
22	CH_3	H	$NHCH(CH_3)_2$	HCl	5,6	206.5–207[e]	57[i]	A–F	$C_{12}H_{21}ClN_2O_3S$	9.07[f]	10.38[g]	11.48	8.96[f]	10.30[g]	11.51
23	n-C_4H_9	H	$NHCH(CH_3)_2$	HCl	5	148.5–151[e]	46	E	$C_{15}H_{27}ClN_2O_3S$	51.34	7.76	10.10	51.26	7.40	9.99
24	p-$CH_3C_6H_4$	H	$NHCH(CH_3)_2$	HCl	6	189.5–190.5[e]	51	E	$C_{18}H_{25}ClN_2O_3S$	56.16	6.55	9.21	55.89	6.65	9.16
25	CH_3	H	$NHCH(CH_3)C_2H_5$	HCl	5	159–161	61	B–E	$C_{13}H_{23}ClN_2O_3S$	48.36	7.18	10.98	48.17	7.15	10.90
26	CH_3	H	$NHCH(CH_3)CH_2OC_6H_5$	Base	5	122–126	36	D	$C_{18}H_{24}N_2O_4S$	59.32	6.64	8.80[g]	59.38	6.65	8.91[g]
27	CH_3	H	$NHC(CH_3)_3$	HBr	5	166–168	81	B–D	$C_{13}H_{23}BrN_2O_3S$	42.50	6.31	7.63[f]	42.46	6.25	7.53[f]
28	CH_3	H	$N(C_2H_5)_2$	Base	5	83.5–87.5	15	G	$C_{13}H_{22}N_2O_3S$	...	9.78[f]	11.19[g]	...	9.59[f]	11.02[g]
29	CH_3	CH_3	$NHCH_3$	HCl	5	217–218	45	A	$C_{11}H_{19}ClN_2O_3S$	44.81	6.50	12.03	44.63	6.55	11.90
30	CH_3	CH_3	$NHCH_3$	HCl	*k*	221.5–222.5	38	A	$C_{11}H_{19}ClN_2O_3S$	44.81	6.50	12.03	44.93	6.40	11.88
31	p-$CH_3C_6H_4$	CH_3	$NHCH_3$	HCl	5	165–168.5	36	D	$C_{17}H_{23}ClN_2O_3S$	55.05	6.25	9.56	55.41	6.42	9.52
32	CH_3	CH_3	$NHCH(CH_3)_2$	HCl	5	228–229[e]	77	A–B	$C_{13}H_{23}ClN_2O_3S$	48.36	7.18	10.98	48.60	7.40	10.89
33	CH_3	CH_3	$NHCH(CH_3)C_2H_5$	HCl	5	190.5–202.5[l]	64	A	$C_{14}H_{25}ClN_2O_3S$	49.91	7.48	9.52[g]	49.84	7.76	9.70[g]
34	CH_3	C_2H_5	$NHCH_3$	HCl	5	234–235[e]	87	A–C	$C_{12}H_{21}ClN_2O_3S$	46.67	6.85	10.38[g]	46.43	6.79	10.65[g]
35	CH_3	C_2H_5	$NHCH(CH_3)_2$	HCl	5	241–243[e]	66	C	$C_{14}H_{25}ClN_2O_3S$	49.91	7.48	10.52	49.62	7.57	10.54

[a] Procedures refer to Experimental Section. [b] A, ethanol; B, ether; C, water; D, absolute ethanol; E, isopropyl alcohol; F, methanol; G, isopropyl ether. [c] Designates the alkyl- or aryl-sulfonamido ring position relative to the ethanolamine side chain. [d] Prepared by a platinum-catalyzed acetone reductive alkylation of 2′-(2-amino-1-hydroxyethyl)methanesulfonanilide. [e] Decomposition. [f] Nitrogen. [g] Sulfur. [h] *Anal.* Calcd.: N, 6.27; S, 7.17. Found: N, 6.16; S, 7.15. [i] Prepared by a platinum-catalyzed acetone reductive alkylation of 3′-(2-amino-1-hydroxyethyl)-*n*-butanesulfonanilide. [j] By procedure 5; similar yield by procedure 6. [k] *threo* form; prepared by two-step process: procedure 6 and then procedure 5. [l] Mixture of diastereoisomeric forms.

Table II

Aminoacylsulfonanilides



R_1	R_2	R_3	R_4	Form	Procedure[a]	Reaction solvent[b]	Time, hr.[c]	M.p., °C. dec.
ortho[d]								
CH_3	H	H	H	$HCl \cdot H_2O$	4	A	16	183.5–184.5
meta[d]								
CH_3	H	H	H	HCl	4	A	16	200–201.5
n-C_3H_9	H	H	H	HCl	4	A	16	199.5–200.5
p-$CH_3C_6H_4$	H	H	H	$HCl \cdot 0.5H_2O$	4	A	16	216.5–217.5
CH_3	H	$CH_2C_6H_5$	CH_3	CH_3SO_3H	1[e]	A	16	205.5–209[f]
C_2H_5	H	$CH_2C_6H_5$	CH_3	$C_2H_5SO_3H$	1	A	16	185–187.5[f]
p-$CH_3C_6H_4$	H	$CH_2C_6H_5$	CH_3	*p*-$CH_3C_6H_4SO_3H$	1	A	16	191–193[f]
CH_3	H	$CH_2C_6H_5$	C_2H_5	CH_3SO_3H	1	A	16	179.5–181.5[f]
CH_3	H	H	$CH_2CH_2C_6H_5$	HCl	4	G	1.0	222.5–224.5
p-$CH_3C_6H_4$	H	H	$CH_2CH_2C_6H_5$	HCl	4	G	0.5	198–200
CH_3	H	$CH_2C_6H_5$	$CH(CH_3)_2$	CH_3SO_3H	1	A	16	178.5–181.5
p-$CH_3C_6H_4$	H	H	$CH(CH_3)_2$	Base	4	G	0.5	148–151
CH_3	H	$CH_2C_6H_5$	$CH(CH_3)CH_2OC_6H_5$[g]	$HCl \cdot 2H_2O$	4	G	1.0	105–114[f]
CH_3	CH_3	$CH_2C_6H_5$	CH_3	HCl	1	A	16	85–115[f]
para[d]								
CH_3	H	H	H	HCl	4	A	3.0[e]	240.5–243
p-$CH_3C_6H_4$	H	H	H	$HCl \cdot 0.5H_2O$	4	A	16	234.5–236
CH_3	H	H	CH_3	HCl	4	I	0.5	236–238
p-$CH_3C_6H_4$	H	$CH_2C_6H_5$	CH_3	Base	4	B	1.0	134.5–138.5[e]
CH_3	H	$CH_2C_6H_5$	$CH_2C_6H_5$	HCl	4[e]	B	5.0	199.5–201.5
CH_3	H	H	$CH(CH_3)_2$	HCl	4	H	0.5	221–223
n-C_3H_9	H	H	$CH(CH_3)_2$	HCl	4	G	1.0	179–180.5
p-$CH_3C_6H_4$	H	H	$CH(CH_3)_2$	HCl	4	G	0.5	233–234.5
CH_3	H	H	$CH(CH_3)C_2H_5$	HCl	4	G	1.0	209–211
CH_3	H	$CH_2C_6H_5$	$CH(CH_3)CH_2OC_6H_5$[g]	HCl	4	G	1.0[e]	119.5–130
CH_3	H	H	$C(CH_3)_3$	HBr	4	G	0.5	218–220
CH_3	H	C_2H_5	C_2H_5	HCl	4	L	0.5[e]	218.5–221.5
CH_3	CH_3	$CH_2C_6H_5$	CH_3	Base	4	G	16	173.5–176.5[e]
p-$CH_3C_6H_4$	CH_3	$CH_2C_6H_5$	CH_3	Na salt	4	G	8.0	>300
CH_3	CH_3	H	$CH(CH_3)_2$	HCl	4	G	5.0	220–222.5
CH_3	CH_3	H	$CH(CH_3)C_2H_5$	Base	4	G	3.0	147–155[f]
CH_3	C_2H_5	$CH_2C_6H_5$	CH_3	Base	4	G	0.5	125.5–127.5[e]
CH_3	C_2H_5	H	$CH(CH_3)_2$	Base	4	G	2.0	186–189

[a] Procedures refer to Experimental Section. [b] A, chloroform; B, acetone; C, water; D, ethanol; E, absolute ethanol; F, ether; G, acetonitrile; H, methanol; I, isopropyl alcohol; J, dioxane; K, isopropyl ether; L, benzene; M, Methyl Cellosolve. [c] With the indicated exceptions, reactions were stirred at room temperature for the indicated time interval. [d] Designates the alkyl- or arylsulfonamido ring position relative to the amino ketone side chain. [e] *Anal.* Calcd.: Cl, 12.54; N, 9.91; H_2O, 6.37. Found: Cl, 12.55; N, 10.02; H_2O, 6.34. [f] Nitrogen. [g] Chlorine. [h] *Anal.* Calcd.: Cl, 10.14; N, 8.01; H_2O, 2.57. Found: Cl, 10.40; N, 7.92; H_2O,

group,[5g] it is noteworthy that except in the case of methoxy and chloro substitution, the biological consequences of these changes have generally lacked significant therapeutic potential. All of these molecular modifications share a common characteristic. Without exception, the substituent replacing the phenolic hydroxyl group exhibits no acidic character. This lack of an acidic proton must certainly affect the reactivity of the substituted phenethanolamine toward an adrenergic receptor site and hence the biological action of such an altered species.

We conjectured that the biological action of a catecholamine might be usefully modified if the phenolic hydroxyl group(s) was replaced with a substituent(s) which would display an acidity comparable to that of a phenol. In addition, the acid-forming elements of this substituent should be capable of spacial orientation so that the geometry of the phenolic hydroxyl group would also be replicated.

One such substituent, which demonstrates the acidic nature of a phenolic hydroxyl, is the alkyl or aryl sulfonamido group. Methanesulfonanilide, for example, is only a slightly stronger acid ($pK_a = 9.9$)[6] than its hydroxyl counterpart, phenol ($pK_a = 11$). This acidity, of course, underlies the basis of the well-known Hinsberg test[7] for differentiation between primary and secondary amines.

Although there appear to be no recorded data concerning the bond angles and bond distances about the nitrogen atom of methanesulfonanilide, it is not unreasonable to assume, on the basis of reported values for other trigonal nitrogen systems, that the phenyl NH unit in methanesulfonanilide should approximate the

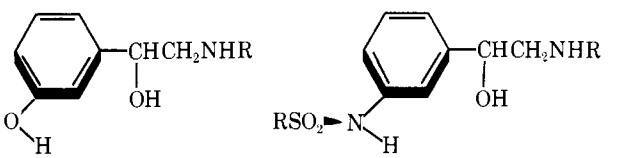
(6) This value, determined in 50% ethanol by potentiometric titration, together with related data will be the subject of a forthcoming publication. R. L. Hinman and B. E. Hoogenboom [*J. Org. Chem.*, **26**, 3461 (1961)] reported a titration $pK_a = 10.8$ for methanesulfonamide itself.

(7) O. Hinsberg, *Ber.*, **23**, 2962 (1890).

Yield, % (pure)	Crystn. solvent[b]	Formula	% calcd. C	% calcd. H	% calcd. S	% found C	% found H	% found S
34	B–C	$C_9H_{13}ClN_2O_3S \cdot H_2O$	38.23	5.35	*e*	38.63	5.71	*e*
54	C–D	$C_9H_{13}ClN_2O_3S$	40.83	4.95	10.58[f]	40.68	4.70	10.29[f]
27	E	$C_{12}H_{19}ClN_2O_3S$	46.97	6.24	11.56[g]	46.90	6.50	11.74[g]
62	C–D	$C_{15}H_{17}ClN_2O_3S \cdot 0.5H_2O$	51.50	5.19	*h*	51.21	6.31	*h*
62	D	$C_{18}H_{24}N_2O_6S_2$	50.45	5.64	14.96	50.63	5.68	15.05
70	D–F	$C_{20}H_{28}N_2O_6S_2$	52.61	6.18	14.04	52.46	6.06	14.03
41	E	$C_{30}H_{32}N_2O_6S_2$	62.05	5.56	11.04	62.14	5.93	10.97
60	D	$C_{19}H_{26}N_2O_6S_2$	51.56	5.92	14.49	51.63	6.03	14.43
18	H	$C_{17}H_{21}ClN_2O_3S$	55.35	5.74	8.69	55.07	5.75	8.92
30	E	$C_{23}H_{25}ClN_2O_3S$	62.08	5.66	7.97[g]	61.83	5.80	8.03[g]
61	E	$C_{20}H_{28}N_2O_6S_2$	52.61	6.18	14.04	52.77	6.26	13.88
65	A	$C_{18}H_{22}N_2O_3S$	62.40[k]	6.40	8.09[f]	61.32	6.60	7.83[f]
67	C–D	$C_{25}H_{29}ClN_2O_4S \cdot 2H_2O$	57.18	6.33	*m*	57.62	6.09	*m*
24[n]	...	$C_{18}H_{23}ClN_2O_3S$	56.46	6.05	9.26[g]	56.40	6.11	9.41[g]
68	C–D	$C_9H_{13}ClN_2O_3S$	13.40[g]	10.58[f]	12.11	13.26[g]	10.26[f]	12.28
62	C–D	$C_{15}H_{17}ClN_2O_3S \cdot 0.5H_2O$	51.50	5.19	*p*	51.41	5.46	*p*
34	C–J	$C_{10}H_{15}ClN_2O_3S$	12.72[g]	10.05[f]	11.50	12.57[g]	9.85[f]	11.38
47	C–I	$C_{23}H_{24}N_2O_3S$	67.62	5.92	6.86[f]	67.33	6.13	6.61[f]
61	D	$C_{23}H_{25}ClN_2O_3S$	62.08	5.66	6.30[f]	62.29	5.71	6.40[f]
27	H	$C_{12}H_{19}ClN_2O_3S$	11.56[g]	9.13[f]	10.45	11.62[g]	8.87[f]	10.53
20	I	$C_{15}H_{25}ClN_2O_3S$	51.64	7.22	10.16[g]	51.75	7.08	10.29[g]
37	E	$C_{18}H_{23}ClN_2O_3S$	56.46	6.05	9.26[g]	56.38	6.24	9.26[g]
59	D	$C_{13}H_{21}ClN_2O_3S$	48.66	6.60	11.05[g]	48.41	6.64	11.04[g]
23	E–K	$C_{25}H_{29}ClN_2O_4S$	61.40	5.98	6.56	61.33	6.45	6.68
58	E–K	$C_{13}H_{21}BrN_2O_3S$	42.74	5.80	8.78	42.96	5.89	8.83
66	H–K	$C_{13}H_{21}ClN_2O_3S$	11.05[g]	8.73[f]	9.99	11.13[g]	8.56[f]	9.65
29	D	$C_{18}H_{22}N_2O_3S$	62.40	6.40	8.09[f]	62.42	6.82	8.26[f]
48	C–G	$C_{24}H_{25}N_2NaO_3S$	64.85	5.67	5.17[r]	64.65	5.93	5.03[r]
40	D	$C_{13}H_{21}ClN_2O_3S$	48.66	6.60	9.99	48.71	6.62	9.84
34	D	$C_{14}H_{22}N_2O_3S$	56.35	7.43	10.74	56.38	7.46	10.59
57	D	$C_{19}H_{24}N_2O_3S$	63.31	6.71	8.89	63.08	6.97	8.83
45	M	$C_{14}H_{22}N_2O_3S$	56.35	7.43	10.74	56.39	7.61	10.67

2.55. [i] Also prepared by procedure 4 in a similar yield. [j] Melts without decomposition. [k] Reduced to **14**, Table I, without further purification. [l] For preparation of N-benzyl-1-phenoxy-2-propylamine see ref. 11. [m] *Anal.* Calcd.: Cl, 6.75; H_2O, 6.86. Found: Cl, 6.81; H_2O, 6.77. [n] Purified by repreparing the hydrochloride from the isolated free base. [o] Refluxed. [p] *Anal.* Calcd.: Cl, 10.14; N, 8.01; H_2O, 2.57. Found: Cl, 10.15; N, 8.23; H_2O, 2.50. [q] Also prepared by procedure 1. [r] Sodium.

phenyl OH unit in phenol, with regard to its spacial geometry.[8] In such a system the alkyl sulfonamido group could align itself, in relation to a receptor site, in a manner closely approximating the phenolic hydroxyl with respect to both bond distances and bond angles. The alkylsulfonyl radical would be presumed to be displaced upward and away from the reactive site. In

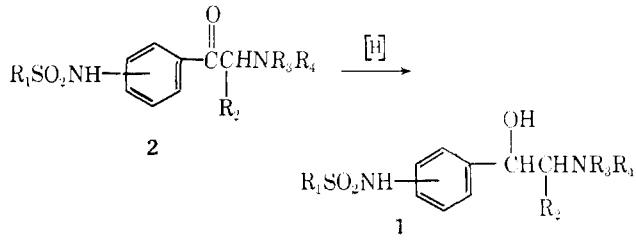


view of these apparent chemical similarities, we have prepared a series of phenethanolamines bearing either an alkyl or arylsulfonamido substituent on the benzene ring.

Chemistry.—All compounds reported in this work are racemic modifications. Since the sulfonamidophenethanolamines (**1**) contain both the acidic sulfonamido and the basic amino functions, they exhibit amphoteric character, forming internal salts as well as alkali-metal and acid-addition salts.

The sulfonamidophenethanolamines (**1**, Table I) were obtained from their 2-aminoacylsulfonanilide precursors (**2**, Table II) by either a palladium-catalyzed

(8) There is almost a complete absence of X-ray crystallographic data directed toward the spacial geometry of the nitrogen atom in sulfonamides. Studies and reviews concerned with the spacial geometry of the sulfonyl group are: L. E. Sutton, Special Publication No. 11, The Chemical Society, London, 1958; S. C. Abrahams, *Quart. Rev.* (London), **10**, 407 (1956); K. N. Trueblood and S. W. Mayer, *Acta Cryst.*, **9**, 628 (1956); and N. K. Kharasch and C. M. Buess, "Organic Sulfur Compounds," Vol. 1, N. K. Kharasch, Ed., Pergamon Press, London, 1961, pp. 541–542. This lack of data relating to the nitrogen atom in sulfonamides is reflected in the fact that, although some atomic-model sets provide special nitrogen atoms for use in construction of carboxamides, no clue is available as to which type of nitrogen atom might be most useful in the construction of the sulfonamide groupings. In view of the considerable theorizing relating to the sulfa drugs, it is most interesting that sulfanilamide itself has only recently been the subject of a complete X-ray study: B. H. O'Conner and E. N. Maslen, *Acta Cryst.*, **18**, 363 (1965); M. Alleaume and J. Decap, *ibid.*, **18**, 731 (1965).



R_1 = methyl, ethyl, butyl, *p*-tolyl
R_2 = H, methyl, ethyl
R_3 = H, methyl, ethyl, isopropyl, *sec*-butyl, *t*-butyl, benzyl, phenethyl, 1-phenoxyisopropyl
R_4 = H, benzyl

low-pressure hydrogenation or a sodium borohydride chemical reduction. Catalytic hydrogenation of the ketones **2** which contained a side-chain amine function bearing a benzyl group were debenzylated concomitantly with reduction of the carbonyl function.[9]

For those sulfonamidophenethanolamines which have two asymmetric carbon atoms (R_2 = alkyl), two racemic modifications are possible. In our hands, catalytic hydrogenation led to a predominance of the *erythro* isomer. In order to obtain a comparison of biological actions, the *threo* racemate (**30**) of *p*-(2-methylamino-1-hydroxypropyl)methanesulfonanilide (**29**) was prepared by first reducing (with sodium borohydride) the intermediate ketone, *p*-(2-benzylmethylaminopropionyl)methanesulfonanilide, to the corresponding carbinol and then debenzylation with palladium-catalyzed hydrogenation. Proof of configuration was obtained by examination of the n.m.r. data (Table III) for the hydrogen–hydrogen interaction on the two adjacent asymmetric centers. Our data for the spin-coupling constants was in accord with that reported by Hyne[10] for the *erythro* and *threo* ephedrines.

Table III
N.m.r. Studies

Compd.	$J_{(H_1,H_2)}$, c.p.s.[a]
Ephedrine[b]	3.6[c,d]
ψ-Ephedrine[e]	9.5[f]
16[b]	3.4
29[b]	3.6
30[e]	9.5
31[b]	3.3
32[e]	3.1
33[b]	3.3
34[e]	4.0
35[b]	3.4[c]

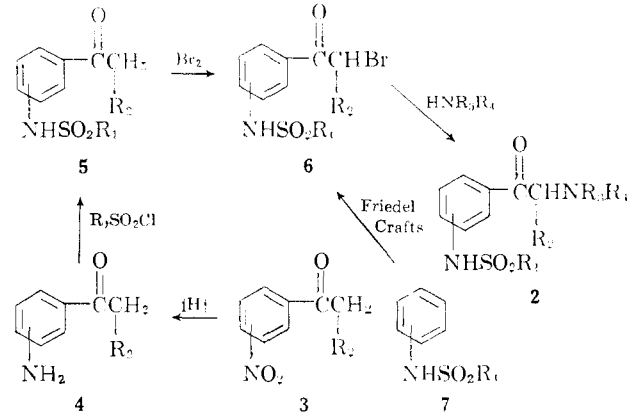
[a] N.m.r. coupling constants for adjacent hydrogen interaction in D_2O was measured on a Varian A-60 instrument using tetramethylsilane as an internal standard at a frequency of 60 Mc.p.s. [b] *erythro* configuration. [c] In trifluoroacetic acid. [d] Lit.[10] coupling constant, 4.0 (chloroform). [e] *threo* configuration. [f] Lit.[10] coupling constant, 8.2 (chloroform).

The failure of Corrodi, *et al.*,[5b] to obtain *threo* racemates by borohydride reduction of their intermediate amino ketones can probably be best explained in light of the studies by Van Dijk and Moed.[11] They suggest that hydride reduction of amino ketones, wherein the amino group bears a hydrogen atom, yields predominantly the *erythro* racemate. In contrast, hydride reduction of amino ketones containing a tertiary amino function yields the *threo* racemate.

It can be assumed, beginning with the first report[12] of the preparation of phenethanolamines having ephedrine-like side chains, that those phenethanolamines arising by hydrogenation of the amino ketones are in the *erythro* series. Not until the advent of hydride reductions has it been possible to prepare, under appropriate conditions, phenethanolamines of the *threo* series directly by reduction of their amino ketone precursors.

Two general and independent methods were developed for the preparation of the ketone precursors **2** of the sulfonamidophenethanolamines. By Scheme I,

Scheme I



the amino function is introduced last, thereby permitting variations of the amino group while holding the sulfonamido moiety constant. With Scheme II, the amine moiety is held constant while the sulfonamido group is varied.

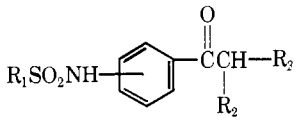
In Scheme I, the ketones **2** were obtained from the reaction of either primary or secondary amines with *o*-, *m*-, and *p*-2-bromoacylsulfonanilides (**6**, Table IV). For those 2-aminoacylsulfonanilides (**2**), where R_2, R_3, and R_4 were hydrogen, the appropriate sulfonamidophenacyl bromides (**6**) were condensed with hexamethylenetetramine providing quaternary ammonium salts which were then converted by acid hydrolysis to the primary aminoacylsulfonanilides (**2**).

The 2-bromoacylsulfonanilide intermediates (**6**) were obtained by either of two ways. By one route, aminophenones (**4**) served as starting materials. Those aminophenones which could not be obtained commercially were prepared by a platinium-catalyzed hydrogenation or a stannous chloride–hydrochloric acid reduction of the appropriate nitrophenones (**3**). Reaction of the aminophenones (**4**) with alkyl- or arylsulfonyl chlorides in pyridine provided the acylsulfonanilides (**5**, Table IV). Subsequent bromination of these *o*-, *m*-, or *p*-acylsulfonanilides (**5**) in ether or chlorinated hydrocarbon solvents furnished the corresponding 2-bromoacylsulfonanilides (**6**). Yields in excess of 70% for the bromination reaction were consistently obtained, and in no instance was aromatic bromination observed.

(9) R. Simonoff and W. H. Hartung, *J. Am. Pharm. Assoc., Sci. Ed.*, **35**, 306 (1946).
(10) J. D. Hyne, *Can. J. Chem.*, **39**, 2563 (1961).
(11) J. Van Dijk and H. D. Moed, *Rec. trav. chim.*, **78**, 22 (1959); **80**, 573 (1961).
(12) J. F. Hyde, E. Browning, and R. Adams, *J. Am. Chem. Soc.*, **50**, 2287 (1928); A. Eberhard, *Arch. Pharm.*, **253**, 62 (1915).

TABLE IV

ACYLSULFONANILIDES



R_1[a]	R_2	R_3	M.p., °C.	Yield, % (pure)	Procedure[b]	Crystn. solvent[c]	Formula	% calcd. C	% calcd. H	% calcd. S	% found C	% found H	% found S
2-CH_3	H	H	105–107	74	1	A	$C_8H_{11}NO_3S$	50.69	5.20	15.03	50.91	5.50	15.18
2-CH_3	H	Br	131–133.5	46	2	A–B	$C_9H_{10}BrNO_3S$	37.00	3.45	10.97	37.14	3.75	10.98
3-CH_3	H	H	96–97.5	49	1	A	$C_8H_{11}NO_3S$	50.69	5.20	15.03	50.89	5.10	14.94
3-CH_3	H	Br	124.5–126	79	2	A	$C_9H_{10}BrNO_3S$	37.00	3.45	10.97	37.30	3.57	10.92
3-n-C_4H_9	H	H	86–87.5	69	1	A–C	$C_{12}H_{17}NO_3S$	56.44	6.71	12.56	56.38	6.63	12.54
3-n-C_4H_9	H	Br	Oil	*d*	2	...	$C_{12}H_{16}BrNO_3S$	...	...	...	...	...	...
3-CH_3	CH_3	H	105.5–107	57	1	D	$C_{10}H_{13}NO_3S$	52.84	5.76	14.11	52.85	5.71	14.21
3-CH_3	CH_3	Br	116.5–118	74	2	A	$C_{10}H_{12}BrNO_3S$	39.22	3.95	10.47	39.36	4.12	10.53
3-*p*-$CH_3C_6H_4$	H	H	130–132[e]	67	1	D	$C_{15}H_{15}NO_3S$	...	...	...	...	...	...
3-*p*-$CH_3C_6H_4$	H	Br	127.5–129.5	50	2	D	$C_{15}H_{14}BrNO_3S$	48.92	3.83	8.71	49.00	4.08	8.75
4-CH_3	H	H	156.5–158.5	75	1	A	$C_9H_{11}NO_3S$	50.69	5.20	15.03	50.68	5.34	14.81
4-CH_3	H	Br	190–191.5[f]	44	3[g]	D	$C_9H_{10}BrNO_3S$	27.35[h]	4.79[i]	10.97	27.35[h]	4.85[i]	11.01
4-CH_3	CH_3	Br	207–209.5[f]	79	3	E	$C_{10}H_{12}BrNO_3S$	39.22	3.95	10.47	39.38	3.93	10.48
4-CH_3	C_2H_5	H	136.5–138	55	1	A	$C_{11}H_{15}NO_3S$	54.75	6.27	13.29	54.75	6.24	13.22
4-CH_3	C_2H_5	Br	143–146	59	2	A	$C_{11}H_{14}BrNO_3S$	41.26	4.41	24.96[h]	41.10	4.58	24.58[h]
4-n-C_4H_9	H	H	103.5–105.5	77	1	A	$C_{12}H_{17}NO_3S$	56.44	6.71	12.56	56.34	6.69	12.44
4-n-C_4H_9	H	Br	122–123.5	52	2	B	$C_{12}H_{16}BrNO_3S$	43.12	4.83	23.91[h]	43.39	5.08	23.80[h]
4-*p*-$CH_3C_6H_4$	H	H	199–200[f]	87	1	D	$C_{15}H_{15}NO_3S$	...	...	...	...	...	...
4-*p*-$CH_3C_6H_4$	H	Br	174–176.5[f]	57	2[k]	E	$C_{15}H_{14}BrNO_3S$	48.92	3.83	8.71	49.17	4.05	8.78
4-*p*-$CH_3C_6H_4$	CH_3	H	185.5–187	66	1	F	$C_{16}H_{17}NO_3S$	63.34	5.65	10.57	63.33	5.83	10.68
4-*p*-$CH_3C_6H_4$	CH_3	Br	167–169	57	2	E	$C_{16}H_{16}BrNO_3S$	50.27	4.22	20.91[h]	49.98	4.33	21.06[h]

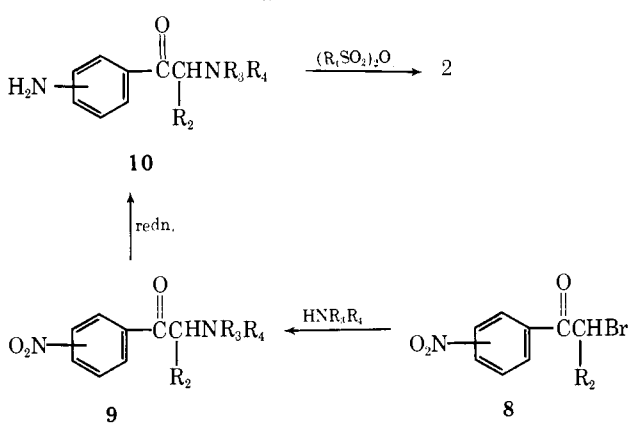
[a] The aromatic ring position of the sulfonamido substituent relative to the acyl side chain is designated by the numerical prefix. [b] Procedures refer to Experimental Section. [c] A, isopropyl alcohol; B, benzene; C, water; D, ethanol; E, acetonitrile; F, acetone. [d] Used without purification. [e] L. A. Elson, C. S. Gibson, and J. D. Johnson [*J. Chem. Soc.*, 1132 (1930)] report m.p. 130°. [f] Decomposition. [g] Also prepared by procedure 2. [h] Bromine. [i] Nitrogen. [j] F. D. Chattaway [*J. Chem. Soc.*, **85**, 391 (1904)] reports m.p. 203°. [k] Also prepared in 5% yield by procedure 3.

By an alternate route, utilizing a Friedel–Crafts reaction, certain of the *p*-2-bromoacylsulfonanilide intermediates (**6**) could be conveniently prepared from the readily available sulfonanilides (**7**). In this manner, 4′-(2-bromoacetyl)methanesulfonanilide was obtained in 90% yield by acylation of methanesulfonanilide with bromoacetyl bromide and aluminum chloride. Haloacylation of *p*-tolylsulfonanilide under similar conditions afforded only a 5% yield of 4′-(2-bromoacetyl)-*p*-tolylsulfonanilide. The *para* orientation[13] of the bromoacetyl electrophile in the haloacylation of sulfonanilides (**7**) was confirmed by the identity of 4′-(2-bromoacetyl)methanesulfonanilide with that obtained from the known 4′-aminoacetophenone (**4**) as outlined in Scheme I.

Reaction of butyryl chloride with methanesulfonanilide yielded two products: 4′-butyrylmethanesulfonanilide and a 15% yield of the diacylated product, 4′-butyryl-N-(methanesulfonyl)butyranilide. The acyl function of this mixed imide was readily removed by mild alkaline hydrolysis.

By Scheme II, the sulfonamidoamino ketone precursors (**2**) were obtained by reaction of alkyl or aryl sulfonic anhydrides with aminoacylaniline derivatives (**10**). The use of sulfonyl chlorides in this reaction was less successful than the use of the corresponding sulfonic acid anhydrides. The intermediates **10** were prepared by a stannous chloride–hydrochloric acid reduction of the corresponding nitro compounds (**9**) which in turn were obtained by condensation of known nitrophenacyl bromides (**8**) with secondary amines.

SCHEME II



Experimental Section[14]

Procedure 1. Mesylation or Equivalent. 3-Propionylmethanesulfonanilide.—3′-Nitropropiophenone (17.9 g., 0.1 mole) in 200 ml. of absolute ethanol was reduced in 1.0 hr. with a Parr hydrogenator (0.2 g. of platinum oxide) to provide a quantitative yield (15.0 g.) of 3′-aminopropiophenone.[15] Mesyl chloride (11.5 g., 0.1 mole) was added dropwise to a stirred solution (held at 10–15°) of 3′-aminopropiophenone (15.0 g., 0.1 mole) in 120 ml. of pyridine. After completing the addition, the mixture was stirred at room temperature for 2 hr., heated to 85°, cooled, and added to 1 l. of water. The aqueous mixture was extracted with 700 ml. of ether and the ethereal solution washed with 200 ml. of 1 *N* HCl then with 400 ml. of 1 *N* NaOH. Acidification of the alkaline extract with concentrated HCl yielded 16.0 g. of product, m.p. 103–105.5°. Crystallization from ethanol afforded analytically pure 3′-propionylmethanesulfonanilide, 12.8 g. (56.5%), m.p. 105.5–107°.

(13) A. G. Kostova, N. N. Tkachenko, and I. I. Evseeva [*J. Gen. Chem. USSR*, **31**, 2091 (1961)] have recently demonstrated the *para* orientation of the Friedel–Crafts product from methanesulfonanilide and acetyl chloride.

(14) Corrected melting points were determined with a Thomas–Hoover capillary apparatus.

(15) B. L. Zenitz and W. H. Hartung [*J. Org. Chem.*, **11**, 446 (1946)] employed a palladium–charcoal catalyst for the preparation of this compound. Our use of this catalyst afforded reduction of the carbonyl as well as the nitro group.

4′-Propionyl-*p*-toluenesulfonanilide.—*p*-Toluenesulfonyl chloride (95.3 g., 0.5 mole) was added portionwise to a stirred pyridine solution (400 ml.) of 4′-aminopropiophenone (79.5 g., 0.5 mole) while maintaining a reaction temperature of 10–15°. After the addition was completed, stirring was continued for 2 hr., and the reaction mixture was poured into 3 l. of ice water giving a solid which was collected and crystallized from ethanol; 130.0 g., m.p. 180–183°. A 10.0-g. portion of this material, crystallized from acetone, afforded 7.7 g. (66% over-all) of analytically pure product, m.p. 185.5–187°.

3′-(2-Benzylmethylaminoacetyl)methanesulfonanilide Methanesulfonate.—2-Benzylmethylamino-3′-nitroacetophenone hydrochloride (17.3 g., 0.053 mole) was added portionwise during 10 min. to a stirred solution (held at 50–60°) of $SnCl_2 \cdot 2H_2O$ (35.8 g., 0.16 mole) in 70 ml. of concentrated HCl. After heating on a steam bath for 4 hr., the mixture was hydrolyzed by mixing with crushed ice containing 400 ml. of 20% NaOH. The crude amine, 2-(benzylmethylamino)-3′-aminoacetophenone, was taken up in 300 ml. of $CHCl_3$, dried ($MgSO_4$), and added to methanesulfonic anhydride[16] (9.2 g., 0.05 mole) in 140 ml. of $CHCl_3$. After standing at room temperature for 16 hr., the separated methanesulfonate salt of 3′-(2-benzylmethylaminoacetyl)-methanesulfonanilide (19 g.) was collected and purified by crystallization from ethanol; yield 14.0 g. (61.8%), m.p. 205.5–209°.

Procedure 2. Bromination of Phenones. 4′-(2-Bromoacetyl)-methanesulfonanilide.—Bromine (8.0 g., 0.05 mole) was added during 45 min. to a stirred suspension of powdered 4′-acetylmethanesulfonanilide (10.6 g., 0.05 mole) and 0.1 g. of benzoyl peroxide in 100 ml. of anhydrous ether.[17] After stirring overnight, the reaction mixture was filtered and the filter cake was washed with ether, isopropyl alcohol, and again with ether leaving an off-white solid, 12.8 g., m.p. 165–175° dec. Three crystallizations from ethanol afforded 4.3 g. (33%) of white needles, m.p. 190–191.5° dec., identical in every respect with 4′-(2-bromoacetyl)methanesulfonanilide prepared by procedure 3.

Procedure 3. Friedel-Crafts Acylation. 4′-(2-Bromoacetyl)-methanesulfonanilide.—Aluminum chloride (40 g., 0.3 mole) was added during 15 min. to a vigorously stirred mixture of methanesulfonanilide[18] (17.1 g., 0.1 mole), bromoacetyl bromide (35.6 g., 0.18 mole), and 75 ml. of CS_2. The mixture was refluxed for 0.5 hr., stirred at room temperature for 1 hr., and left overnight. The CS_2 layer was decanted and the dark, red-brown, viscous complex was hydrolyzed by pouring onto crushed ice containing 7 ml. of concentrated HCl. The brown product was collected and washed with water, ethanol, and finally ether to yield 26.5 g. of tan solid, m.p. 161–171° dec. Crystallization from ethanol afforded 12.7 g. (44%) of analytically pure product, m.p. 190–191.5° dec.

4′-Butyrylmethanesulfonanilide.—Aluminum chloride (400 g., 3.0 moles) was added during 1 hr. (so as to maintain a temperature of 30–35°) to a stirred solution of methanesulfonanilide (171 g., 1.0 mole) and butyryl chloride (180 g., 1.7 moles) in 800 ml. of CS_2. After refluxing for 2 hr. and hydrolyzing with ice and dilute HCl, 307 g. of material melting at 75–80° was collected. Extraction of the crude product with 1.5 l. of 1 *N* NaOH and acidification of the basic extract with concentrated HCl provided 4′-butyrylmethanesulfonanilide, 160 g., m.p. 130–135°. The analytical sample melted at 136.5–138° (2-propanol).

The alkali-insoluble material (45 g., 15%), crystallized from 2-propanol, afforded pure **4′-butyryl-N-(methanesulfonyl)butyrylanilide,** m.p. 120.5–122°.

Anal. Calcd. for $C_{15}H_{21}NO_4S$: C, 57.85; H, 6.80; S, 10.30. Found: C, 57.88; H, 7.09; S, 10.55.

Hydrolysis of this mixed imide by warming with 1 *N* NaOH until solution occurred and subsequent acidification with HCl gave additional 4′-butyrylmethanesulfonanilide.

Procedure 4. Amination of Phenacyl Bromides. 3′-(2-Aminoacetyl)methanesulfonanilide Hydrochloride.—The following procedure with slight variations is essentially that of Mannich and Hahn.[19] A mixture of 3′-(2-bromoacetyl)methanesulfonanilide (43.8 g., 0.15 mole) and excess hexamethylenetetramine (31.5 g., 0.23 mole) in 1 l. of $CHCl_3$, stirred for 16 hr. at room temperature, provided $CHCl_3$-insoluble [(3-methanesulfonamido)-benzoyl]methylhexamethylenetetraammonium bromide, 63 g., (97.5%), m.p. 167–168° dec. Hydrolysis was effected by a brief heating (*ca.* 3 min.) of 60 g. (0.14 mole) of the adduct in 1.4 l. of ethanol and 70 ml. of concentrated HCl. Filtration, cooling, collection of the first crop, concentration of the filtrate to 200 ml., and dilution with 1.2 l. of ether gave a combined yield of 55.5 g. of crude material. Trituration of this material with 100 ml. of cold water gave 30.5 g. of product which, when crystallized from 80% ethanol, afforded 19.8 g. (54%) of analytically pure 3′-(2-aminoacetyl)methanesulfonanilide hydrochloride, m.p. 200–201.5° dec.

4′-(2-Isopropylaminoacetyl)methanesulfonanilide Hydrochloride.—Powdered 4′-(2-bromoacetyl)methanesulfonanilide (14.6 g., 0.05 mole) was added in small portions to a stirred solution (held at 15°) of isopropylamine (11.8 g., 0.2 mole) in 30 ml. of methanol. After stirring for 0.5 hr. at room temperature, the solution was concentrated. The viscous, red-yellow residue was dissolved in 150 ml. of acetone and acidified with ethanolic HCl to give 11.4 g. of product. Crystallization from methanol yielded analytically pure product as white plates, 4.2 g. (27%), m.p. 221–225° dec.

4′-(2-Benzylmethylaminopropionyl)methanesulfonanilide.—A mixture of 4′-(2-bromopropionyl)methanesulfonanilide (30.6 g., 0.1 mole) and *N*-methylbenzylamine (24.0 g., 0.2 mole) in 400 ml. of acetonitrile was stirred for 16 hr. The acetonitrile was removed under vacuum and the residue was extracted with 500 ml. of warm acetone. Concentration of the acetone extract and crystallization of the residual yellow solid from ethanol provided 14 g. of the free base, m.p. 163–169° dec. This impure product was taken up in 100 ml. of 1 *N* HCl and filtered. Neutralization of the filtrate with concentrated NH_4OH gave 4′-(2-benzylmethylaminopropionyl)methanesulfonanilide which was crystallized from ethanol to analytical purity: 10.1 g. (29.2%), m.p. 173.5–176.5°.

4′-(2-Dibenzylaminoacetyl)methanesulfonanilide hydrochloride was prepared in acetone from 4′-(2-bromoacetyl)methanesulfonanilide (29.2 g., 0.1 mole) and dibenzylamine (39.4 g., 0.2 mole) as described in the preceding example. The reaction mixture was filtered from dibenzylamine hydrobromide and the filtrate was concentrated. Solution of the base in 200 ml. of ethanol and 1 l. of ether followed by treatment with ethanolic HCl provided 39 g. of the hydrochloride salt. Crystallization from ethanol afforded the pure product, 27 g. (60.8%), m.p. 199.5–201.5° dec.

2-(Benzylmethylamino)-3′-nitropropiophenone Hydrochloride.—*N*-Methylbenzylamine (53.6 g., 0.44 mole) was added dropwise to a stirred solution of 2-bromo-3′-nitropropiophenone[20] (57.2 g., 0.22 mole) in 300 ml. of acetonitrile held at 15–20°. After standing at room temperature for 16 hr., the solution was concentrated under vacuum, and the residue was extracted with 500 ml. of ether. The water-washed and dried ($MgSO_4$) ethereal extract was acidified with ethanolic HCl to yield a tacky solid which on trituration with acetone provided 65.5 g. of crude hydrochloride. Crystallization from 1:1 ethanol-ether, then from 1:3 dimethylformamide–ether gave pure 2-(benzylmethylamino)-3′-nitropropiophenone hydrochloride, 48.9 g. (66%), m.p. 168–172.5° dec.

Anal. Calcd. for $C_{17}H_{19}ClN_2O_3$: C, 60.98; H, 5.72; Cl, 10.59. Found: C, 60.93; H, 6.14; Cl, 10.42.

The 2-(benzyl-, methyl-, ethyl-, and isopropyl-substituted amino)-3′-nitroacetophenone hydrochlorides were obtained by condensation of 2-bromo-3′-nitroacetophenone[21] and the appropriate *N*-benzylalkylamine. With 2-benzylmethylamino-3′-nitroacetophenone, the purified hydrochloride had m.p. 191–193° dec., lit.[22] m.p. 173–174° dec.

Anal. Calcd. for $C_{16}H_{17}ClN_2O_3$: C, 59.90; H, 5.34; Cl, 11.05. Found: C, 59.69; H, 5.61; Cl, 11.04.

Procedure 5. Hydrogenation of Aminoacylsulfonanilides. 3′-(2-Methylamino-1-hydroxyethyl)methanesulfonanilide Methanesulfonate.—3′-(2-Benzylmethylaminoacetyl)methanesulfonanilide methanesulfonate (8.6 g., 0.2 mole) in 200 ml. of absolute methanol was reduced in a Parr hydrogenator employing 0.6 g. of 10% palladium-charcoal. After removal of the catalyst and

(16) For preparation of sulfonic anhydrides see L. Field, *J. Am. Chem. Soc.*, **74**, 394 (1952); L. Field and P. Settlage, *ibid.*, **76**, 1222 (1954).

(17) The utility of benzoyl peroxide as a free-radical reaction initiator in the bromination of sulfonamidoacylphenones (**5**) appeared to be of questionable value; this was found to be the case with either chlorinated hydrocarbons or ether as reaction solvents.

(18) C. S. Marvel, M. D. Helfrick, and J. P. Belsley, *J. Am. Chem. Soc.*, **51**, 1272 (1929).

(19) C. Mannich and F. L. Hahn, *Ber.*, **44**, 1542 (1911).

(20) J. W. Baker, *J. Chem. Soc.*, 1155 (1932).

(21) W. L. Evans and B. T. Brooks, *J. Am. Chem. Soc.*, **30**, 406 (1908).

(22) S. I. Sergievskaya and L. E. Sventsitskaya, *J. Gen. Chem. USSR*, **26**, 2195 (1956).

solvent, the residue (6.53 g., m.p. 192–201°) was crystallized from ethanol to analytical purity; yield 5.1 g. (75%), m.p. 207–209°.

Neutralization of the above salt with aqueous NaOH, concentration, and trituration with cold water afforded the free base, m.p. 159–161°.

Anal. Calcd. for $C_{10}H_{16}N_2O_3S$: C, 49.16; H, 6.60; S, 13.12. Found: C, 49.06; H, 6.52; S, 13.11.

Solution of the free base in methanol with a stoichiometric quantity of sodium methoxide followed by dilution with ether afforded the **sodium salt**, m.p. 249–251° dec.

Anal. Calcd. for $C_{10}H_{15}N_2NaO_3S$: C, 45.10; H, 5.68; N, 10.52; Na, 8.6. Found: C, 45.34; H, 5.97; N, 10.41; Na, 8.4.

Acidification of a 2-propanol solution of the free base with ethanolic HCl afforded the hydrochloride salt, m.p. 154–155.5°.

Anal. Calcd. for $C_{10}H_{16}N_2O_3S \cdot HCl$: C, 44.81; H, 6.50; S, 10.88. Found: C, 45.00; H, 6.75; S, 10.95.

***threo*-4′-(2-Methylamino-1-hydroxypropyl)methanesulfonanilide Hydrochloride.**—The ethanol solution of *threo*-4′-(2-benzylmethylamino-1-hydroxypropyl)methanesulfonanilide hydrochloride, obtained by procedure 6, was charged with 15 g. of 10% palladium-charcoal catalyst and debenzylated in a Parr hydrogenator. The reaction mixture was filtered and the filter cake was extracted with 500 ml. of hot methanol. Concentration of the combined ethanol and methanol fractions gave 59.6 g. of white solid which, when crystallized from ethanol, afforded 24.4 g. (37%) of analytically pure product, m.p. 221.5–222.5°.

Procedure 6. Hydride Reduction of Aminoacylsulfonanilides. 4′-(2-Isopropylamino-1-hydroxyethyl)-*p*-toluenesulfonanilide Hydrochloride.—Sodium borohydride (1.27 g., 0.034 mole) was added during 20 min. to 4′-(2-isopropylaminoacetyl)-*p*-toluenesulfonanilide hydrochloride (6.5 g., 0.017 mole) in 60 ml. of methanol at 10–15°. After stirring for 10 min. the mixture was acidified with ethanolic HCl, the insoluble material was collected, and the filtrate was concentrated to dryness. Crystallization of the residue from isopropyl alcohol afforded 3.1 g. (51%) of analytically pure product, m.p. 189.5–190.5° dec.

***threo*-4′-(2-Benzylmethylamino-1-hydroxypropyl)methanesulfonanilide Hydrochloride.**—Sodium borohydride (16.8 g., 0.44 mole) was added (stirring) during 0.5 hr. to 4′-(2-benzylmethylaminopropionyl)methanesulfonanilide (76 g., 0.22 mole) in 22 ml. (0.22 mole) of 10 *N* NaOH and 650 ml. of methanol held at 10–15°. After stirring overnight, the solution was concentrated under vacuum. The residue was then taken up in 250 ml. of absolute ethanol and acidified with ethanolic HCl, and the mixture was filtered from NaCl. Without further purification, *threo*-4′-(2-benzylmethylamino-1-hydroxypropyl)methanesulfonanilide hydrochloride was debenzylated by procedure 5.

Biological Results and Discussion

Although both methanesulfonanilide and phenol are weak acids of about the same strength, it cannot be assumed that the simplicity of this single chemical parameter will carry over to complexities of the adrenergic system and sympathomimetic amine action. At the present stage of development, it is convenient and necessary to use selected *in vitro* and *in vivo* assays as guides in revealing the biological profile of a sympathomimetic amine. Rigorous comparisons on the basis of such highly stylized mechanical responses tend to ignore, however, factors relating to selective distribution of the drug, relative effects on the metabolism and membrane properties of the effector cell, and effects on transport, duration, and distribution of endogenous amines.

The concept of dual adrenergic receptors, as proposed by Ahlquist,[23] is employed in the following discussion to delineate sympathomimetic action. Primary screening was designed to reveal β-receptor stimulation and blockage and α-receptor stimulation and blockage. For these purposes, relaxation of the uterine horn from diestrus rats, immersed in Tyrode solution at 38°, was used as an initial *in vitro* test for β-receptor stimulation. Blockade of β-receptor was measured by the antagonistic action of the compounds toward isoproterenol relaxation of the isolated guinea pig tracheal spiral, suspended in Tyrode solution and held at 37°. Potent α-receptor stimulation was revealed by examination of the spasmogenic action of the compounds on the isolated, quiescent rat seminal vesicle suspended in Locke-Ringer solution held at 38°. Blockade of α-receptor was measured by the antagonistic action of the compounds toward norepinephrine-induced spasms of the rat seminal vesicle preparation. Gross cardiovascular effects were obtained by the intravenous infusion of the test compounds into sodium thiopental–sodium barbital anesthetized dogs. Taken alone, pressor and depressor events are not an ideal screening test response, in that they are the composite of changes in splanchnic, skeletal muscle, skin, and other vascular bed blood volumes, together with inotropic and chronotropic changes in cardiac function.

Those compounds which contain an alkyl- or arylsulfonamido group *meta* to the lateral ethanolamine side chain (Table V) are α- or β-receptor stimulants, depending upon the size of the substituent groups. Compound **6** is a highly active relatively pure α-receptor stimulant. This substance is a potent direct stimulant of the rat seminal vesicle and the cat nictitating membrane. Its actions are blocked by the α-adrenergic

TABLE V

SYMPATHOMIMETIC AND BLOOD PRESSURE ACTION OF THE *m*-SULFONAMIDOPHENETHANOLAMINES[a]

	Sympathomimetic effects					
	α-Receptor[b]		β-Receptor[b]		Blood pressure effects[b]	
Compd. no.	Stimulant EC_{50}, g./ml.[c]	Blockade IC_{50}, g./ml.[d]	Stimulant EC_{50}, g./ml.[e]	Blockade (× DCI)[f]	Dose, mg./kg.[g]	Response, %
3	320	...	60	0.07	0.02	↑ 30
4	...	105	800	0.07	2.0	↓ 15
5	...	190	140	0.04	10.0	↓ 48
6	2.8	...	0.4	0.1	0.01	↑ 20
7	68	...	0.2	0.05	0.01	↑ 22
8	...	195	0.7	0.09	7.0	↓ 25
9	1500	...	0.02	0.1	0.3	↑ 25
10	...	40	0.3	0.1	0.5	↓ 5
11	...	13	0.02	0.07	9.0	↓ 13
12	...	100	0.01	1.0	0.07	↓ 10
13	...	97	0.7	0.1	0.2	↓ 10
14	...	79	0.002	1.1	0.9	↓ 20
15	...	2.05	0.003	0.03	0.5	↓ 5
16	380	...	150	0.1	0.6	↑ 25

[a] The pharmacological data has been calculated for the concentration of the sulfonamidophenethanolamine bases. [b] For a description of the test methods see ref. 16 and 18. [c] Concentration required to produce contractions of the rat seminal vesicle 50% as intense as that of *l*-epinephrine (2.0 μg./ml.). [d] Concentration required to reduce by 50% the contraction of the rat seminal vesicle induced by *l*-norepinephrine (4.0 μg./ml.). [e] Concentration required to reduce by 50% the spontaneous contractions of the rat uterus. [f] Relative β-blocking action as a multiple of the activity of dichloroisoproterenol (DCI = 1) measured by the concentration required to inhibit by 50% the relaxant action of isoproterenol (0.01 μg./ml.) on the guinea pig tracheal spiral. [g] Minimal effective dose producing a significant blood pressure response in the dog.

(23) R. P. Ahlquist, *Am. J. Physiol.*, **153**, 586 (1948).

blocker, phentolamine. In addition, **6**[24] showed a marked lack of effectiveness as a β-receptor stimulant. Gross blood-pressure effects are about half those of the optically active phenolic phenethanolamine, phenylephrine.

Any departure from the structure of **6** resulted in a decrease of α-adrenergic action. This was reflected in both the cardiovascular and *in vitro* assays. With compound **15**, wherein the lateral amine substituent is the phenoxyisopropyl group, while retaining the *m*-methanesulfonamido substituent, the pharmacological profile has changed from that of a typical α-stimulant to that of β-stimulation. This compound contained about 10–15% the activity of *l*-epinephrine on the rat uterus and exhibited a moderate depressor action in the anesthetized dog.

For those phenethanolamines bearing the alkyl- or arylsulfonamido substituent *para* to the ethanolamine side chain, the dominant biological effect was one of β-receptor blockage (Table VI). Outstanding in this

Table VI

Adrenergic β-Receptor Effects of the *p*-Sulfonamidophenethanolamines[a]

Compd.	Stimulation[b] IC_{50}, μg./ml.[c]	Blockade[b] (× DCI)[d]	Compd.	Stimulation[b] IC_{50}, μg./ml.[c]	Blockade[b] (× DCI)[d]
17	>350	0.2	27	>1600	24.2
18	360	0.03	28	>400	...
19	>1800	0.2	29	>180	2.4
20	1.2	0.06	30	>180	0.001
21	>360	0.01	31	110	0.03
22	>900	6.0	32	>10	1.3
23	1100	0.03	33	>20	0.3
24	>90	0.2	34	>20	0.1
25	>10	1.3	35	>20	0.4
26	195	4.0			

[a] The pharmacological data has been calculated for the concentration of the sulfonamidophenethanolamine bases. [b] For a description of the test methods see ref. 18. [c] Concentration required to reduce by 50% the spontaneous contractions of the rat uterus. [d] Relative β-blocking action as a multiple of the activity of dichloroisoproterenol (DCI = 1) measured by the concentration required to inhibit by 50% the relaxant action of isoproterenol (0.01 μg./ml.) of the guinea pig tracheal spiral.

respect were compounds **22**, **26**, **27**, and **29**. Compound **22**, which possesses an isopropylamino substituent, demonstrated six times the β-receptor blockage potency of dichloroisoproterenol in the *in vitro* guinea pig tracheal spiral test. The *erythro* racemate of compound **29** was somewhat less active than **22**. Interestingly, it has a small N-methylamino substituent in conjunction with an α-methyl grouping, whereas all other reported β-blocking agents have either a characteristic isopropyl- or *t*-butylamino substituent.[25] Compound **30**, which is the *threo* racemate of **29**, was considerably less active as a β-adrenergic blocking agent than the *erythro* form (**29**). It would appear, therefore, that for sulfonamidophenethanolamines with ephedrine-like side chains, adrenergic β-blocking action is more pronounced with those having the *erythro* configuration as is evidently the case of catecholamine sympathomimetic action.

Compound **27** with a lateral *t*-butylamine substituent, although effective in blocking the classical responses to β-receptor stimulation, *e.g.*, smooth or cardiac muscle responses, exhibits a relatively flat dose–response curve in these situations. However, this profile was absent with the biochemical responses to sympathetic stimulation, hyperglycemia, and mobilization of free fatty acids, and steep straight dose–response curves were obtained.

Aside from β-receptor blockage, the *p*-sulfonamidophenethanolamines were singularly inactive in other preparations, exhibiting no significant β-receptor stimulant action or CNS effects.[26]

The *o*-sulfonamidophenethanolamines (**1** and **2**) have considerably less sympathomimetic activity than their *meta* or *para* analogs.

All of the compounds that exhibit a positive classical pharmacologic effect demonstrate a toxicity which is an extension of their pharmacologic action. Although those compounds with the more intense biological effects exhibit the greater toxicity, there is no evidence that the alkyl- or arylsulfonamido group itself introduces any unusual parameter into the toxicological pattern of sympathomimetic amines. Also, it would appear that the insignificant central nervous system involvement of the sulfonamidophenethanolamines may be attributed to their marked polar character.

Metabolic studies suggest that the alkylsulfonamido substituent does not serve as an efficient substrate to some of the biochemical events relating to the eventual destruction of the catecholamines. By virtue of this fact, the apparent longer duration of action of these substances as contrasted to their phenolic counterparts can be rationalized. This difference is also reflected in a comparison of the *in vitro vs.* the corresponding *in vivo* effects. The sulfonamidophenethanolamines often demonstrate a greater relative potency *in vivo* when compared to their phenolic counterparts.

Compound **6**, 3′-(2-methylamino-1-hydroxyethyl)-(methanesulfonanilide)[27] (amidephrine), has been investigated in the clinic and has been shown to be an effective, nonirritating, long-acting, nasal decongestant.[28] The β-receptor blocking agents: **22**, 4′-(2-isopropylamino-1-hydroxyethyl)methanesulfonanilide[27]; **27**, 4′-[2-(*t*-butylamino)-1-hydroxyethyl]methanesulfonanilide[27]; and **29**, 4′-(2-methylamino-1-hydroxypropyl)methanesulfonanilide,[27] are undergoing clinical examination.

(24) For detailed pharmacological studies of compound **6** see H. C. Stanton, K. W. Dungan, and P. M. Lish, *Intern. J. Neuropharmacol.*, **4**, 235 (1965); K. W. Dungan, H. C. Stanton, and P. M. Lish, *ibid.*, **4**, 219 (1965).

(25) See ref. 5a and 5d; J. S. Stephenson, British Patent 909,357 (Oct. 31, 1962); J. W. Black and J. S. Stephenson, *Lancet*, **2**, 311 (1962); J. J. Burns and K. I. Colville, *Pharmacologist*, **4**, 178 (1962); B. Levy, *J. Pharmacol. Exptl. Therap.*, **146**, 129 (1964); J. W. Black, A. F. Crowther, R. G. Shanks, L. H. Smith, and A. C. Dornhurst, *Lancet*, **1**, 1080 (1964); J. J. Burns, K. I. Colville, L. A. Lindsay, S. P. April, and R. A. Salvador, Fall Meeting of the American Society of Pharmacology and Experimental Therapeutics, Lawrence, Kansas, 1964, Abstracts of Papers, p. 118.

(26) For a detailed discussion of the pharmacology and toxicology of the β-receptor blocking agents **22** and **29** see P. M. Lish, J. H. Weikel, and K. W. Dungan, *J. Pharmacol. Exptl. Therap.*, **149**, 161 (1965); H. C. Stanton, T. Kirchgessner, and K. Parmenter, *ibid.*, **149**, 174 (1965); D. C. Kvam and D. A. Riggilo, *ibid.*, **149**, 183 (1965).

(27) The following designations have already been cited in biological literature for these compounds: **6**, MJ-1996; **22**, MJ-1999; **27**, MJ-1985; and **29**, MJ-1998.

(28) N. D. Fabricant, D. I. Frank, and A. H. Neffson, *Eye, Ear, Nose, Throat Monthly*, **43**, 39 (1964).

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Synthesis and Properties of 5-Mercaptomethyluracil and Related Derivatives[1]

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Reaction of 5-hydroxymethyluracil with the appropriate hydrogen halide afforded 5-chloro-, -bromo-, or -iodomethyluracil. Treatment of 5-chloromethyluracil with thioacetamide in dimethylformamide solution led to 5-acetiminothiomethyluracil hydrochloride from which 5-mercaptomethyl- and 5-acetylthiomethyluracil were obtained by alcoholysis or by hydrolysis. Alkaline solutions of 5-mercaptomethyluracil and its acetyl derivative gave 5-methyl- and 5-ethylthiomethyluracil upon reaction with methyl and ethyl iodide, and 5-benzylthiomethyluracil was obtained with benzyl chloride. 5-Chloromethyluracil reacted with potassium thiocyanate, thiourea, thioglycolic acid, ammonium dithiocarbamate, and benzyl mercaptan to yield 5-thiocyanomethyluracil, 5-(S-thioureido)methyluracil hydrochloride, 5-carboxymethylthio-, 5-(S-dithiocarbamyl)-, and 5-benzylthiomethyluracil, respectively. Condensation of 5-chloro- and 5-mercaptomethyluracil led to bis(thyminyl) sulfide, which was oxidized to its sulfone. Upon oxidation of 5-mercaptomethyluracil and its acetyl derivative, bis(thyminyl) disulfide was obtained. These 5-halogeno- and 5-mercaptomethyluracils were transformed to thymine with tin and hydrochloric acid or with Raney nickel. Some physical and chemical properties of the new compounds are described. 6-Mercaptomethyluracil showed a marked inhibitory activity on mouse Ehrlich carcinoma (fluid form) and complete inhibition of Krebs II (ascitic) tumor.

The occurrence of 5-hydroxymethyluracil and 5-hydroxymethylcytosine in DNA and the hydroxymethylation reactions involved in the biosynthesis of such pyrimidines, as well as thymine,[2] prompted the study of the synthesis of new derivatives of these substances which might affect growth. Analogs of these compounds which manifest powerful inhibitory activity in biological systems, and even exhibit antitumor and antiviral effects, include 5-fluorouracil,[3] 5-trifluoromethyluracil,[4] 5-fluorocytosine[5] and their nucleosides, and 5-iododeoxyuridine.[6] In the course of this study, methods were developed for the synthesis of 5-monohalogeno and 5-mercapto derivatives of 5-hydroxymethyluracil and these are described in this report.

Very few derivatives of mercaptomethylpyrimidines have been described previously.[7] These include 4-amino-5-mercaptomethylpyrimidine[8] and 4-mercaptomethyl-5-phenoxyuracil,[9] which could only be synthesized by laborious procedures. There has been a report of the preparation of thyminylcysteine obtained by the interaction of 5-hydroxymethyluracil (I) and cysteine in HCl.[10]

In an extension of previous studies of the introduction of sulfur into purines,[11,12] 5-chloromethyluracil (II) (Scheme I) was converted into a variety of mercaptomethyl derivatives by reaction with thioacetamide and other thio reagents. Earlier synthesis of II were accomplished in 57% yield, by the chloromethylation of uracil with trioxymethylene in concentrated HCl at 80°, and in 37% yield by treatment of 5-hydroxymethyluracil (I) with hot HCl.[13] The synthesis of II was achieved in greater yield (90%) by simple reaction of I with concentrated HCl at room temperature. 5-Bromo- (III) and 5-iodomethyluracil (IV) were obtained in a similar manner from I with concentrated HBr and HI in quantitative and 82% yield, respectively.[14] Treatment of 5-chloromethyluracil (II) with HI below 0° led also to the iodo derivative IV in 91% yield.[15]

When a solution of 5-chloromethyluracil (II) and thioacetamide[16] in dimethylformamide was heated at

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(2) (a) G. R. Wyatt and S. S. Cohen, *Nature*, **170**, 1072 (1952); (b) S. S. Cohen, J. Lichtenstein, H. D. Barner, and M. Green, *J. Biol. Chem.*, **228**, 611 (1957); (c) M. Green, H. D. Barner, and S. S. Cohen, *ibid.*, **228**, 621 (1957); (d) R. G. Kallen, M. Simon, and J. Marmur, *J. Mol. Biol.*, **5**, 248 (1962).

(3) For a review on 5-fluorouracil, *cf.* R. E. Handschumacher and A. D. Welch in "The Nucleic Acids," Vol. III, E. Chargaff and J. N. Davidson, Ed., Academic Press Inc., New York, N. Y., 1960, p. 498.

(4) C. Heidelberger, D. G., Parsons, and D. C. Remy, *J. Med. Chem.*, **7**, 1 (1964).

(5) R. Duschinsky and E. Pleven, *J. Am. Chem. Soc.*, **79**, 4559 (1957).

(6) (a) E. C. Herrmann, Jr., *Proc. Soc. Exptl. Biol. Med.*, **107**, 142 (1961); (b) H. D. Kaufman, *ibid.*, **109**, 251 (1962).

(7) *Cf.* D. J. Brown, "The Pyrimidines," Interscience Publishers, Inc. New York, N. Y., 1962, p. 277.

(8) M. Horiuchi and Y. Sawa, *J. Pharm. Soc. Japan*, **78**, 137 (1958).

(9) T. B. Johnson and A. J. Hill, *Am. Chem. J.*, **48**, 296 (1912).

(10) R. E. Cline, R. M. Fink, and K. Fink, *J. Am. Chem. Soc.*, **81**, 2521 (1959).

(11) A. Giner-Sorolla, E. Thom, and A. Bendich, *J. Org. Chem.*, **29**, 3209 (1964).

(12) A. Giner-Sorolla and A. Bendich, *J. Med. Chem.*, **8**, 667 (1965).

(13) (a) W. A. Skinner, M. G. M. Schelstraete, and R. B. Baker, *J. Org. Chem.*, **25**, 149 (1960); (b) J. A. Carbon, *ibid.*, **25**, 1731 (1960); (c) J. H. Burckhalter, R. J. Seiwald, and H. C. Scarborough, *J. Am. Chem. Soc.*, **82**, 991 (1960).

(14) 5-Bromomethyluracil was previously prepared in 79% yield from I and hydrogen bromide in glacial acetic acid (*cf.* ref. 13b).

(15) *Cf.* (a) E. Fischer, *Ber.*, **31**, 2550 (1898); (b) G. B. Elion and G. H. Hitchings, *J. Am. Chem. Soc.*, **78**, 3510 (1956).

(16) (a) Thioacetamide should be considered predominantly as a zwitterion, $CH_3C(S^{\ominus})=NH_2^{\oplus}$: *cf.* E. Allenstein and P. Quis, *Chem. Ber.*, **97**, 3162 (1964). (b) For a review on thionamides, *cf.* R. N. Hurd and G. DeLaMater, *Chem. Rev.*, **61**, 45 (1961).