Sulfonanilides. II. Analogs of Catecholamines[1,2]

A. A. LARSEN, WILLIAM A. GOULD, HERBERT R. ROTH, WILLIAM T. COMER, ROBERT H. ULOTH,

Department of Chemistry

K. W. DUNGAN, AND P. M. LISH

Department of Pharmacology, Mead Johnson Research Center, Mead Johnson and Company, Evansville, Indiana 47721

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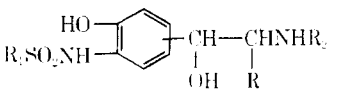
Two isomeric series of substituted phenethanolamines have been prepared. Compounds of these series contain a hydroxyl group and our new bioisostere, the alkanesulfonamido moiety, substituted on the benzene ring. Compounds from one of these series, wherein the alkanesulfonamido substituent is *meta* and the hydroxyl group is *para* to the ethanolamine side chain, are potent α and β adrenergic agonists. In the other series, wherein the phenolic hydroxyl group and the alkanesulfonamido are transposed, the adrenergic action is considerably less. The hypothesis offered to explain this difference in activity is based on the necessity for an absolute, spatially oriented, interdependence between both the catechol and amine portions of catecholamines and the entire receptor complimentarity. The preparation of the compounds is discussed, pharmacological screening data are presented, and structure-activity specificities and potencies are examined.

In part I of this series,[3] the rationale for the use of the alkyl- or arylsulfonamido substituent in place of the phenolic hydroxyl group was introduced and demonstrated. Incorporation of this new bioisosteric group into the benzene ring of suitably constituted phenethanolamines was shown to confer either adrenergic stimulant or adrenergic blocking activity to these substances. In the case of sympathomimetic amines, the alkanesulfonamido group can, apparently by virtue of its acidity and spacial geometry, elicit some of the same biological phenomena as the phenolic hydroxyl group. We have now investigated a series of compounds which bear both an alkanesulfonamido and hydroxyl group in the benzene ring of phenethanolamines. These substances (I) can be considered analogous to the catecholamines, norepinephrine, epinephrine, isoproterenol, etc.

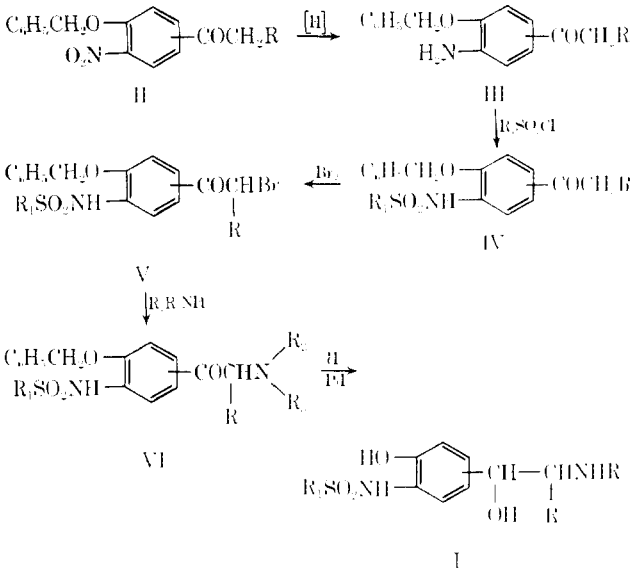


I

Chemistry.—Two series of compounds are reported here: one of them, the *meta* series, has the alkanesulfonamido group *meta* and the phenolic hydroxyl group *para* relative to the ethanolamine side chain; in the second, the *para* series, the positions of the alkanesulfonamido and phenolic hydroxyl groups are reversed in relation to the ethanolamine side chain.[4]

As outlined in Scheme I, the two series of compounds were prepared in the same general manner.

SCHEME I



R = H, CH_3, C_2H_5; R_2 = alkyl, aralkyl, aryloxyalkyl; R_1 = CH_3, n-C_4H_9; R_3 = H, $C_6H_5CH_2$.

The benzyloxynitrophenones (II) were reduced to their corresponding aminobenzyloxyphenones (III) using either Raney nickel and hydrazine hydrate[5] or platinum oxide and hydrogen (Table I).

The anilines (III) were allowed to react with an alkanesulfonyl chloride in the presence of pyridine alone or triethylamine with benzene as a solvent. In a single instance, with pyridine, the yield was depressed because the anilide (IV) was isolated as a salt of the reactant aniline (III). In a few other instances, bismesylated anilines were also obtained. As these are insoluble in cold alkali, they were readily separated from the alkali-soluble monomesylated products (IV). The bismesylated anilines are easily hydrolyzed by warming with dilute alkali to give the desired monomesylated anilines.[3]

The phenacyl bromides (V) were prepared by bromination of the acylalkanesulfonanilides (IV) in methylene chloride solution.

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

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

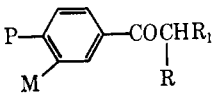
(3) Solfonanilides. I: R. H. Uloth, J. R. Kirk, W. A. Gould, and A. A. Larsen, *J. Med. Chem.*, **9**, 88 (1966).

(4) These compounds are related to catecholamines and are also conveniently called phenethanolamines. However, more precise chemical nomenclature dictates that these substances be named as derivatives of alkanesulfonanilides. In order that the generic and individual names be more clearly defined, the following relationships are cited. The compounds for these two specific examples are analogous to norepinephrine: (a) *meta* series, 4-hydroxy-3-methanesulfonami,lophenethanolamine = 5'-(2-amino-1-hydroxyethyl)-2'-hydroxymethanesulfonanilide; (b) *para* series, 3-hydroxy-4-methanesulfonami,lophenethanolamine = 4'-(2-amino-1-hydroxyethyl)-2'-hydroxymethanesulfonanilide.

(5) D. Balcom and A. Furst, *J. Am. Chem. Soc.*, **75**, 4334 (1953).

TABLE I

PHENONE INTERMEDIATES



P	M	R	R_1	Prepn method[a]	Yield, %	Crystn solvent[b]	Mp, °C	Formula	%C Calcd	%C Found	%H Calcd	%H Found	%N Calcd	%N Found
$C_6H_5CH_2O$	NO_2	H	H	1A	80	B-C	135.5-137	$C_{15}H_{13}NO_4$	66.41	66.17	4.83	4.86	5.16	5.16
$C_6H_5CH_2O$	NO_2	CH_3	H	1A	48	A	109.5-110.5	$C_{16}H_{15}NO_4$	67.36	67.33	5.30	5.60	4.91	4.97
$C_6H_5CH_2O$	NO_2	C_2H_5	H	1A	56	B	95-98	$C_{17}H_{17}NO_4$	68.21	67.93	5.73	5.49	4.68	4.76
HO	NH_2	H	H	2B	98	D	225-225.5 dec	$C_8H_9NO_2 \cdot HCl$	48.86[c]	48.64	5.64	5.61	7.12	7.21
$C_6H_5CH_2O$	NH_2	H	H	2A	87	A	127.5-129	$C_{15}H_{15}NO_2$	74.66	74.95	6.27	6.32	5.81	5.89
$C_6H_5CH_2O$	NH_2	CH_3	H	2B	89	A	127-128	$C_{16}H_{17}NO_2$	75.27	75.04	6.71	6.86	5.49	5.58
$C_6H_5CH_2O$	NH_2	C_2H_5	H	2B	79	B	84-86	$C_{17}H_{19}NO_2$	75.81	76.05	7.11	7.19	5.20	5.17
HO	CH_3SO_2NH	H	H	3A	76	D	205.5-206.5	$C_9H_{11}NO_4S$	47.15	47.11	4.84	4.99	6.11	5.04
$C_6H_5CH_2O$	CH_3SO_2NH[d]	H	H	3B	84	A	141.5-142.5	$C_{16}H_{17}NO_4S$	60.17	60.14	5.37	5.40	4.38	4.31
$C_6H_5CH_2O$	CH_3SO_2NH	CH_3	H	3B	87	A	137.5-138.5	$C_{17}H_{19}NO_4S$	61.24	61.23	5.74	5.70	4.20	4.20
$C_6H_5CH_2O$	CH_3SO_2NH	C_2H_5	H	3B	86	A	113.5-116.5	$C_{18}H_{21}NO_4S$	62.22	62.24	6.09	6.13	9.23[e]	9.48
HO	n-$C_4H_9SO_2NH$	H	H	3A	68	A	156.5-158.5	$C_{12}H_{17}NO_4S$	53.12	53.31	6.32	6.32	5.16	5.24
$C_6H_5CH_2O$	n-$C_4H_9SO_2NH$	H	H	3A	77	A	98-100	$C_{19}H_{23}NO_4S$	63.13	63.21	6.41	6.36	8.87[e]	9.03
HO	CH_3SO_2NH	H	Br	4	70	A	210-211	$C_9H_{10}BrNO_4S$	35.08	35.12	3.27	3.36	4.55	4.52
$C_6H_5CH_2O$	CH_3SO_2NH	H	Br	4	85	A	118.5-121.5	$C_{16}H_{16}BrNO_4S$	48.25	47.79	4.05	4.36	8.05[e]	7.71
$C_6H_5CH_2O$	CH_3SO_2NH	CH_3	Br	4	95	A	144-146	$C_{17}H_{18}BrNO_4S$	49.52	49.43	4.40	4.68	3.40	3.29
$C_6H_5CH_2O$	CH_3SO_2NH	C_2H_5	Br	4	94	A	95.5-97.5	$C_{18}H_{20}BrNO_4S$	50.71	50.75	4.73	5.03	7.52[e]	7.52
HO	n-$C_4H_9SO_2NH$	H	Br	4	86	A	184.5-185.5	$C_{12}H_{16}BrNO_4S$	41.15	41.35	4.60	4.68	4.00	4.17
$C_6H_5CH_2O$	n-$C_4H_9SO_2NH$	H	Br	4	88	A	121.5-123.5	$C_{19}H_{22}BrNO_4S$	51.82	52.12	5.04	5.06	7.28[e]	7.49
NO_2	$C_6H_5CH_2O$	H	H	1B	62	B	96.5-98.5	$C_{15}H_{13}NO_4$	66.41	66.01	4.83	4.76	5.16	5.21
NH_2	$C_6H_5CH_2O$	H	H	2A	70	A	79-81	$C_{15}H_{15}NO_2$	74.66	74.44	6.27	6.55	5.81	5.80
CH_3SO_2NH	$C_6H_5CH_2O$	H	H	3B	55	A	146.5-147.5	$C_{16}H_{17}NO_4S$	60.17	60.11	5.37	5.39	4.38	4.30
CH_3SO_2NH	$C_6H_5CH_2O$	H	Br	4	95	A	166-168	$C_{16}H_{16}BrNO_4S$	48.25	47.48	4.05	4.28	3.52	3.32

[a] Corresponds to procedure given in Experimental Section. [b] A, 2-propanol; B, isopropyl ether; C, 2-butanone; D, ethanol. [c] Hemihydrate. [d] The dimesylated compound 5′-acetyl-2′-benzyloxydimethanesulfonanilide, mp 180.5–182°, was also isolated. *Anal.* Calcd for $C_{17}H_{19}NO_6S_2$: C, 51.37; H, 4.82; N, 3.53; S, 16.13. Found: C, 51.33; H, 4.99; N, 3.71; S, 15.86. [e] Sulfur.

In general, the aminophenones (VI) were obtained by condensation of the phenacyl bromides (V) with the appropriate secondary benzylamine or primary amine. For those aminophenones (VI) where R, R_1, and R_2 are hydrogen, the phenacyl bromide (V) could be condensed with hexamethylenetetramine providing a quaternary salt which was then hydrolyzed in dilute acid to the primary aminophenone. Our observations support those of Suter and Ruddy,[6] that condensation of hexamethylenetetramine with a phenacyl halide only occurs when R is hydrogen. For those primary phenethanolamines (I) where R is alkyl, the precursor amino ketones (VI) were prepared with a blocking group incorporated into the amino moiety. The benzhydryl blocking group was preferred over dibenzyl because it underwent a more facile hydrogenolysis.

Purification of the aminophenones was often difficult since there is a tendency for these substances to hydrate. In addition, compounds **28** and **31–33** possess two centers of carbon asymmetry. No attempt was made to purify these aminophenones to the point where it was certain that only one racemate was present. In some instances, the amino ketones never did give satisfactory analyses, yet could be used for conversion to the phenethanolamines (I). The aminoacylhydroxysulfonanilides (VI) are listed in Table II.

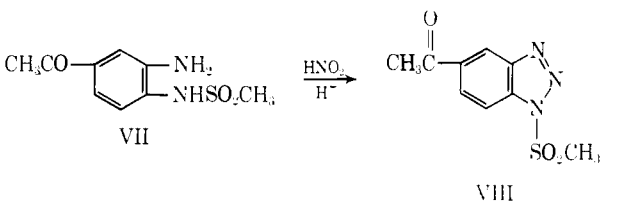
Catalytic hydrogenation (Pd–C) of the aminophenones (VI) resulted in reduction of the carbonyl group to the secondary hydroxyl function and removal of any benzyl or benzhydryl groups present in the molecule. Alternatively, the aminophenones (VI) can be reduced first with $NaBH_4$ and then the protective benzyl groups removed by catalytic hydrogenolysis. The resultant (2-amino-1-hydroxyalkyl)hydroxyalkanesulfonanilides (I) are listed in Table III.

(6) C. M. Suter and A. W. Ruddy, *J. Am. Chem. Soc.*, **66**, 747 (1944).

The preparation of the hydroxynitrophenones for the two series of compounds required different synthetic procedures. For the *meta* series, 4′-hydroxyphenones were nitrated with red fuming nitric acid at −25° to yield the 4′-hydroxy-3-nitrophenones.[7] These phenolic phenones were allowed to react with benzyl chloride in the presence of KOH to give the 4′-benzyloxy-3′-nitrophenones (II). Most of the phenethanolamines (I) were prepared from intermediates wherein the phenolic hydroxyl group had been converted to the benzyl ether. For the *meta* series, the entire sequence of reactions, depicted in Scheme I, can be accomplished without protecting the phenolic hydroxyl group.

For the *para* series, initial consideration was given to the direct acylation of 2′-alkoxy- or 2′-benzyloxyalkanesulfonanilides. The results from this approach were equivocal. A second unsuccessful attempt, involving diazotization of 4′-acetyl-2′-aminomethanesulfonanilide (VII) gave an alkali-insoluble material, the structure of which is apparently the triazole VIII (Scheme II).[8]

SCHEME II



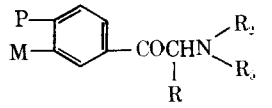
VII VIII

The synthesis of 3′-benzyloxy-4′-nitroacetophenone was successfully accomplished in the manner illustrated in Scheme III.

(7) P. D. Bartlett and E. N. Trachtenberg, *ibid.*, **80**, 5808 (1958); F. C. Brown, *ibid.*, **68**, 272 (1946).

(8) K. Sasse, R. Wegler, and F. Grewe, U. S. Patent 2,943,017 (June 28, 1960), have described the preparation of a number of analogous methanesulfonyltriazoles by diazotization of 2′-aminomethanesulfonanilides.

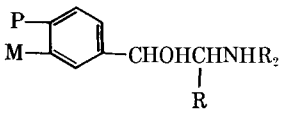
TABLE II: AMINOACYLHYDROXYSULFONANILIDES



No.	P	M	R	R_2	R_3	Reaction temp (°C)/ time (hr)	Yield, %	Purification solvent[a]	Mp, °C	Formula	% C Calcd	% C Found	% H Calcd	% H Found	% S Calcd	% S Found
1	$C_6H_5CH_2O$	CH_3SO_2NH	H	H	H	25/18	61	A	226–228 dec	$C_{16}H_{18}N_2O_4S \cdot HCl$	50.50[b]	50.32	5.31	5.22	8.44	8.30
2	$C_6H_5CH_2O$	CH_3SO_2NH	H	$C_6H_5CH_2$	$C_6H_5CH_2$	25/18	49	B	120.5–126.5 dec	$C_{30}H_{30}N_2O_4S$	68.81[b]	68.92	5.97	6.06	6.12	6.34
3	$C_6H_5CH_2O$	CH_3SO_2NH	CH_3	$C_6H_5CH_2$	$C_6H_5CH_2$	82/2	69	A	137.5–139.5	$C_{31}H_{32}N_2O_4S$	70.43	70.50	6.10	6.35	6.06	6.26
4	$C_6H_5CH_2O$	CH_3SO_2NH	C_2H_5	$(C_6H_5)_2CH$	H	88/24	79	G–C	186.5–188.5 dec	$C_{31}H_{33}N_2O_4S \cdot HCl$	65.88	65.89	5.88	5.98	5.67	5.57
5	$C_6H_5CH_2O$	n-$C_4H_9SO_2NH$	H	$(C_6H_5)_2CH$	H	25/5	46	E–C	187.5–189.5 dec	$C_{32}H_{34}N_2O_4S \cdot HCl$	66.36	66.64	6.09	6.13	5.54	5.58
6	$C_6H_5CH_2O$	CH_3SO_2NH	H	$C_6H_5CH_2$	CH_3	25/4	41	D	123.5–125.5	$C_{24}H_{26}N_2O_4S$	65.73	65.36	5.98	6.38	7.31	7.31
7	$C_6H_5CH_2O$	CH_3SO_2NH	CH_3	$C_6H_5CH_2$	CH_3	25/3	59	B	119–121	$C_{25}H_{28}N_2O_4S$	66.35	66.57	6.24	6.52	7.08	7.00
8	$C_6H_5CH_2O$	CH_3SO_2NH	C_2H_5	$C_6H_5CH_2$	CH_3	25/24	79	...	Oil	$C_{26}H_{30}N_2O_4S \cdot HCl$	[c]					
9	$C_6H_5CH_2O$	n-$C_4H_9SO_2NH$	H	$C_6H_5CH_2$	CH_3	25/4	31	...	178–186	$C_{27}H_{32}N_4O_4S \cdot HCl$	[c]					
10	$C_6H_5CH_2O$	CH_3SO_2NH	H	$C_6H_5CH_2$	$(CH_3)_2CH$	25/18	74	A	104–110	$C_{26}H_{30}N_2O_4S$	[c]					
11	$C_6H_5CH_2O$	CH_3SO_2NH	CH_3	$C_6H_5CH_2$	$(CH_3)_2CH$	82/2	21	A–B	114–116	$C_{27}H_{32}N_2O_4S$	67.47	67.34	6.71	6.87	6.67	6.82
12	$C_6H_5CH_2O$	CH_3SO_2NH	C_2H_5	H	$(CH_3)_2CH$	25/3	36	F	185–190	$C_{21}H_{28}N_2O_4S \cdot HCl$	[c]					
13	$C_6H_5CH_2O$	n-$C_4H_9SO_2NH$	H	H	$(CH_3)_2CH$	25/0.5	47	A–C	173.5–176.5 dec	$C_{22}H_{30}N_2O_4S \cdot HCl$	58.07	57.99	6.87	7.00	7.04	7.19
14	HO	CH_3SO_2NH	H	H	$(CH_3)_3C$	25/1	75	E–C	236–238 dec	$C_{19}H_{26}N_2O_4S \cdot HCl$	46.35	46.18	6.28	6.50	9.52	9.49
15	$C_6H_5CH_2O$	CH_3SO_2NH	CH_3	$C_6H_5CH_2$	$HOCH_2CH_2$	25/24	30	A–C	177–180	$C_{26}H_{30}N_2O_5S \cdot HCl$	[c]					
16	$C_6H_5CH_2O$	CH_3SO_2NH	H	H	$C_6H_5CH_2CH_2$	25/1	50	E–C	213.5–214.5	$C_{24}H_{26}N_2O_4S \cdot HCl$	60.68	60.67	5.73	6.14	6.75	6.80
17	$C_6H_5CH_2O$	CH_3SO_2NH	CH_3	H	$C_6H_5CH_2CH_2$	25/18	71	A	213.5–215.5	$C_{25}H_{28}N_2O_4S \cdot HCl$	61.40	61.16	5.98	6.22	6.55	6.62
18	$C_6H_5CH_2O$	CH_3SO_2NH	C_2H_5	H	$C_6H_5CH_2CH_2$	15/3	52	B	176–178	$C_{26}H_{30}N_2O_4S \cdot HCl$	62.07	62.09	6.21	6.47	6.37	6.49
19	$C_6H_5CH_2O$	n-$C_4H_9SO_2NH$	H	H	$C_6H_5CH_2CH_2$	15/1	43	B	195–198 dec	$C_{27}H_{31}N_2O_4S \cdot HCl$	62.71	62.42	6.43	6.23	6.20	6.42
20	$C_6H_5CH_2O$	CH_3SO_2NH	CH_3	H	$4\text{-}CH_3C_6H_4CH_2CH_2$	25/2	72	E–C	219–221 dec	$C_{26}H_{30}N_2O_4S \cdot HCl$	62.07	62.02	6.21	6.50	6.37	6.45
21	$C_6H_5CH_2O$	CH_3SO_2NH	CH_3	H	$4\text{-}CH_3OC_6H_4CH_2CH_2$	25/2	72	E–C	215.5–218 dec	$C_{26}H_{30}N_2O_5S \cdot HCl$	60.16	60.46	6.02	6.22	6.18	6.33
22	$C_6H_5CH_2O$	CH_3SO_2NH	C_2H_5	H	$4\text{-}CH_3OC_6H_4CH_2CH_2$	25/4	68	B	176.5–178.5	$C_{27}H_{32}N_2O_5S \cdot HCl$	60.83	60.91	6.24	6.31	6.01	6.19
23	$C_6H_5CH_2O$	n-$C_4H_9SO_2NH$	H	H	$4\text{-}CH_3OC_6H_4CH_2CH_2$	25/1	69	B	191.5–193.5	$C_{28}H_{34}N_2O_5S \cdot HCl$	61.46	61.63	6.45	6.44	5.86	5.97
24	$C_6H_5CH_2O$	CH_3SO_2NH	CH_3	H	$4\text{-}CH_3SO_2NHC_6H_4CH_2CH_2$	25/3	26	G	210.5–211.5 dec	$C_{26}H_{31}N_3O_6S_2 \cdot HCl$	52.83[b]	52.91	5.63	5.91	10.85	10.99
25	$C_6H_5CH_2O$	CH_3SO_2NH	CH_3	H	$4\text{-}ClC_6H_4CH_2CH_2$	25/2	70	E–C	214–216 dec	$C_{25}H_{25}ClN_2O_4S \cdot HCl$	57.36	57.39	5.38	5.71	6.12	6.34
26	$C_6H_5CH_2O$	CH_3SO_2NH	H	H	$3,4\text{-}(CH_3O)_2C_6H_3CH_2CH_2$	25/1	34	E–C	183.5–185 dec	$C_{26}H_{30}N_2O_6S \cdot HCl$	58.36	58.34	5.84	6.01	5.99	6.22
27	$C_6H_5CH_2O$	CH_3SO_2NH	CH_3	H	$3,4\text{-}(CH_3O)_2C_6H_3CH_2CH_2$	25/2	27	B	170.5–171.5	$C_{27}H_{32}N_2O_6S \cdot HCl$	59.06	58.75	6.06	6.31	5.84	5.77
28	$C_6H_5CH_2O$	CH_3SO_2NH	CH_3	H	$4\text{-}CH_3OC_6H_4CH_2CH(CH_3)$	25/4	24	A–E	212–214	$C_{27}H_{32}N_2O_5S \cdot HCl$	59.82[b]	59.86	6.32	6.42	5.91	6.05
29	$C_6H_5CH_2O$	CH_3SO_2NH	H	H	$3,4\text{-}(CH_3O)_2C_6H_3CH_2CH(CH_3)$	25/1	25	A–C	160–164	$C_{27}H_{32}N_2O_6S \cdot HCl$	58.10[b]	57.81	6.14	6.19	5.74	5.75
30	$C_6H_5CH_2O$	CH_3SO_2NH	H	H	$3,4\text{-}(CH_2O_2)C_6H_3CH_2CH(CH_3)$	25/2	21	H	200–202 dec	$C_{26}H_{28}N_2O_6S \cdot HCl$	58.58	58.67	5.48	5.63	6.01	6.16
31	$C_6H_5CH_2O$	CH_3SO_2NH	CH_3	H	$3,4\text{-}(CH_2O_2)C_6H_3CH_2CH(CH_3)$	25/16	30	A–E	222–224	$C_{27}H_{30}N_2O_5S \cdot HCl$	58.31[b]	58.54	5.80	6.02	5.77	5.97
32	$C_6H_5CH_2O$	CH_3SO_2NH	CH_3	$C_6H_5CH_2$	$C_6H_5OCH_2CH(CH_3)$	82/24	50	A	161–163	$C_{33}H_{36}N_2O_5S \cdot HCl$	65.06	65.06	6.12	6.25	5.26	5.26
33	$C_6H_5CH_2O$	CH_3SO_2NH	C_2H_5	H	$C_6H_5OCH_2CH(CH_3)$	82/16	87	F	43–75	$C_{27}H_{32}N_2O_5S$	[c]					
34	$C_6H_5CH_2O$	CH_3SO_2NH	CH_3	$-(CH_2)_5-$		82/16	74	A–B	192.5–194.5	$C_{22}H_{28}N_2O_4S \cdot HCl$	58.32	58.20	6.45	6.63	7.08	7.05
35	CH_3SO_2NH	$C_6H_5CH_2O$	H	H	H	25/1	59	A	196.5–198 dec	$C_{16}H_{18}N_2O_4S \cdot HCl$	50.59[b]	51.16	5.31	5.29	8.44	8.57
36	CH_3SO_2NH	$C_6H_5CH_2O$	H	$C_6H_5CH_2$	$C_6H_5CH_2$	25/18	47	B	130–145	$C_{30}H_{30}N_2O_4S$	[c]					
37	CH_3SO_2NH	$C_6H_5CH_2O$	H	$C_6H_5CH_2$	CH_3	25/1	47	A	118–125	$C_{24}H_{26}N_2O_4S$	[c]					
38	CH_3SO_2NH	$C_6H_5CH_2O$	H	$C_6H_5CH_2$	$(CH_3)_2CH$	25/24	26	A–D	181.5–183.5 dec	$C_{28}H_{30}N_2O_4S \cdot HCl$	59.93[b]	60.12	6.38	6.52	6.15	6.00
39	CH_3SO_2NH	$C_6H_5CH_2O$	H	H	$C_6H_5CH_2CH_2$	25/2	26	B–C	204–212 dec	$C_{23}H_{26}N_2O_4S \cdot HCl$	[c]					
40	CH_3SO_2NH	$C_6H_5CH_2O$	H	H	$4\text{-}CH_3OC_6H_4CH_2CH_2$	25/2	24	B–C	196–198	$C_{24}H_{28}N_2O_5S \cdot HCl$	59.45	59.43	5.79	6.00	6.35	6.48

[a] A, ethanol; B, 2-propanol; C, isopropyl ether; D, diethyl ether; E, methanol; F, acetone; G, acetonitrile; H, 2-butanone. [b] Hemihydrate. [c] Satisfactory analyses were not obtained on material used for reduction to phenethanolamines. [d] Monohydrate.

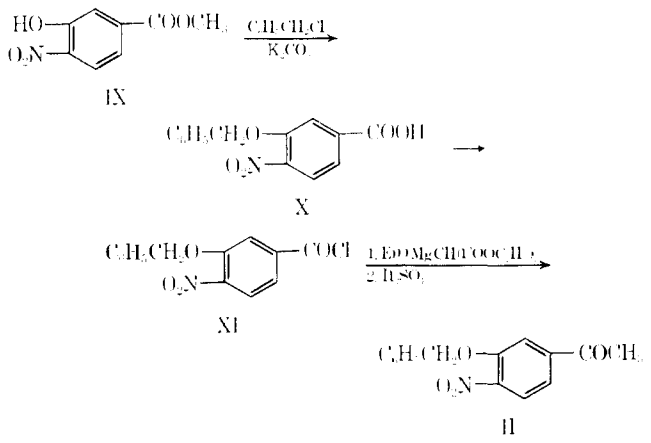
TABLE III: ALKANESULFONAMIDOHYDROXYPHENETHANOLAMINES



No.	P	M	R	R_2	Precursor	Yield, %	Crystn solvent[g]	Mp, °C	Formula	C Calcd	C Found	H Calcd	H Found	S Calcd	S Found
41	HO	CH_3SO_2NH	H	H	1, 2	78[e]	A–C	173.5–174 dec	$C_9H_{14}N_2O_4S\cdot HCl$	38.23	38.24	5.35	5.44	11.34	11.27
42	HO	CH_3SO_2NH	CH_3	H	3	85	B–D	201–202.5 dec	$C_{10}H_{16}N_2O_4S\cdot HCl$	40.47	40.68	5.78	5.98	10.80	10.56
43	HO	CH_3SO_2NH	C_2H_5	H	4	85	A–C	208–209 dec	$C_{11}H_{18}N_2O_4S\cdot HCl$	42.51	42.69	6.16	6.35	10.32	10.37
44	HO	*n*-$C_4H_9SO_2NH$	H	H	5	88	E	172–173	$C_{12}H_{20}N_2O_4S\cdot HCl$	44.37	44.53	6.52	6.51	9.87	10.01
45	HO	CH_3SO_2NH	H	CH_3	6	65	A–C	198–199 dec	$C_{10}H_{16}N_2O_4S\cdot HCl$	40.47	40.78	5.78	5.76	10.80	10.75
46	HO	CH_3SO_2NH	CH_3	CH_3	7	80	B–C	219.5–220.5 dec	$C_{11}H_{18}N_2O_4S\cdot HCl$	42.51	42.71	6.16	6.20	10.31	10.17
47	HO	CH_3SO_2NH	C_2H_5	CH_3	8	50	B–C	163–165.5	$C_{12}H_{20}N_2O_4S\cdot HCl$	44.37	44.46	6.52	6.47	9.87	10.05
48	HO	*n*-$C_4H_9SO_2NH$	H	CH_3	9	80	E–C	150–153	$C_{13}H_{22}N_2O_4S\cdot HCl$	46.08	45.78	6.84	7.13	9.46	9.15
49	HO	CH_3SO_2NH	H	$(CH_3)_2CH$	10	32	A–C	195.5–196.5 dec	$C_{12}H_{20}N_2O_4S\cdot HCl$	44.37	44.58	6.52	6.56	9.87	9.74
50	HO	CH_3SO_2NH	CH_3	$(CH_3)_2CH$	11	60	F	203.5–205.5 dec	$C_{13}H_{22}N_2O_4S\cdot HCl$	46.08	46.34	6.84	6.84	9.46	9.58
51	HO	CH_3SO_2NH	C_2H_5	$(CH_3)_2CH$	12	79	A-C	213–214 dec	$C_{14}H_{24}N_2O_4S\cdot HCl$	47.65	47.56	7.14	7.18	9.08	8.76
52	HO	*n*-$C_4H_9SO_2NH$	H	$(CH_3)_2CH$	13	75	B–C	150–151.5	$C_{15}H_{26}N_2O_4S\cdot HCl$	49.10	48.89	7.42	7.39	8.74	8.74
53	HO	CH_3SO_2NH	H	$(CH_3)_3C$	14	84	A–C	221.5–222.5 dec	$C_{13}H_{22}N_2O_4S\cdot HCl$	46.08	46.28	6.84	7.00	9.46	9.59
54	HO	CH_3SO_2NH	CH_3	$HOCH_2CH_2$	15	86	A–C	182.5–184	$C_{12}H_{20}N_2O_5S\cdot HCl$	42.28	41.99	6.21	6.35	9.41	9.31
55	HO	CH_3SO_2NH	H	$C_6H_5CH_2CH_2$	16	73	A–C	205–205.5 dec	$C_{17}H_{22}N_2O_4S\cdot HCl$	52.77	52.42	5.99	6.13	8.29	8.28
56	HO	CH_3SO_2NH	CH_3	$C_6H_5CH_2CH_2$	17	80	B–C	186–188	$C_{18}H_{24}N_2O_4S\cdot HCl$	53.92	53.42	6.28	6.33	8.00	7.97
57	HO	CH_3SO_2NH	C_2H_5	$C_6H_5CH_2CH_2$	18	63	A–C	195.5–197.5 dec	$C_{19}H_{26}N_2O_4S\cdot HCl$	54.99	54.86	6.56	6.78	7.73	7.84
58	HO	*n*-$C_4H_9SO_2NH$	H	$C_6H_5CH_2CH_2$	19	61	A–C	189.5–190.5 dec	$C_{20}H_{28}N_2O_4S\cdot HCl$	55.99	55.91	6.81	6.99	7.47	7.51
59	HO	CH_3SO_2NH	CH_3	4-$CH_3C_6H_4CH_2CH_2$	20	81	A–C	218–219 dec	$C_{19}H_{26}N_2O_4S\cdot HCl$	54.99	55.03	6.56	6.52	7.73	7.72
60	HO	CH_3SO_2NH	CH_3	4-$CH_3OC_6H_4CH_2CH_2$	21	73	A–C	181–183	$C_{19}H_{26}N_2O_5S\cdot HCl$	52.95	52.68	6.32	6.53	7.44	7.58
61	HO	CH_3SO_2NH	C_2H_5	4-$CH_3OC_6H_4CH_2CH_2$	22	74	A–C	192–193.5	$C_{20}H_{28}N_2O_5S\cdot HCl$	53.98	53.99	6.57	6.61	7.20	7.35
62	HO	*n*-$C_4H_9SO_2NH$	H	4-$CH_3OC_6H_4CH_2CH_2$	23	53	A–C	191.5–192.5 dec	$C_{21}H_{30}N_2O_5S\cdot HCl$	54.95	54.73	6.81	7.12	6.98	7.04
63	HO	CH_3SO_2NH	CH_3	4-$CH_3SO_2NHC_6H_4CH_2CH_2$	24	71	A–C	226-227 dec	$C_{19}H_{27}N_3O_6S_2\cdot HCl$	46.19	46.01	5.71	5.92	12.98	12.99
64	$C_6H_5CH_2O$	CH_3SO_2NH	CH_3	4-$ClC_6H_4CH_2CH_2$[a]	25	32	A–B	208.5–210 dec	$C_{25}H_{29}ClN_2O_4S\cdot HCl$	57.14	56.88	5.75	5.79	6.10	6.19
65	$C_6H_5CH_2O$	CH_3SO_2NH	CH_3	4-$ClC_6H_4CH_2CH_2$[b]	25	24	F	178–180	$C_{25}H_{29}ClN_2O_4S\cdot HCl$	57.14	57.40	5.75	5.83	6.10	6.24
66	HO	CH_3SO_2NH	H	3,4-$(CH_3O)_2C_6H_3CH_2CH_2$	26	72	A–C	185–186 dec	$C_{19}H_{26}N_2O_6S\cdot HCl$	51.06	50.67	6.09	6.12	7.17	7.18
67	HO	CH_3SO_2NH	CH_3	3,4-$(CH_3O)_2C_6H_3CH_2CH_2$	27	77	A–C	203–204 dec	$C_{20}H_{28}N_2O_6S\cdot HCl$	52.11	52.19	6.34	6.44	6.95	7.17
68	HO	CH_3SO_2NH	CH_3	4-$CH_3OC_6H_4CH_2CH(CH_3)$	28	75	B–C	199.5–200.5	$C_{20}H_{28}N_2O_5S\cdot HCl$	52.91[h]	53.02	6.66	6.45	7.06	7.16
69	HO	CH_3SO_2NH	H	3,4-$(CH_3O)_2C_6H_3CH_2CH(CH_3)$	29	57	A-C	184–185	$C_{20}H_{28}N_2O_6S\cdot HCl$	52.11	51.83	6.34	6.40	6.95	6.91
70	HO	CH_3SO_2NH	H	3,4-$(CH_2O_2)C_6H_3CH_2CH(CH_3)$	30	65	F	167–168	$C_{19}H_{24}N_2O_6S\cdot HCl$	51.29	51.41	5.66	5.77	7.21	7.33
71	HO	CH_3SO_2NH	CH_3	3,4-$(CH_2O_2)C_6H_3CH_2CH(CH_3)$	31	76	B–C	198.5–200.5	$C_{20}H_{26}N_2O_6S\cdot HCl$	52.33	52.12	5.93	6.10	6.98	7.11
72	HO	CH_3SO_2NH	CH_3	$C_6H_5OCH_2CH(CH_3)$[c]	32	68	G	228.5–229.5 dec	$C_{19}H_{26}N_2O_5S\cdot HCl$	52.95	52.72	6.32	6.44	7.44	7.62
73	HO	CH_3SO_2NH	CH_3	$C_6H_5OCH_2CH(CH_3)$[c]	32	11	B	202.5–204	$C_{19}H_{26}N_2O_5S\cdot HCl$	52.95	52.77	6.32	6.45	7.44	7.54
74	HO	CH_3SO_2NH	C_2H_5	$C_6H_5OCH_2CH(CH_3)$	33	21	A–C	178.5–180	$C_{20}H_{28}N_2O_5S\cdot HCl$	53.98	54.23	6.57	6.48	7.20	7.22
75	HO	CH_3SO_2NH	CH_3	*d*	34	73	B	230.5–231.5 dec	$C_{18}H_{24}N_2O_4S\cdot HCl$	49.37	49.69	6.91	6.92	8.79	8.83
76	CH_3SO_2NH	HO	H	H	35, 36	59[f]	E	185.5–186.5 dec	$C_9H_{14}N_2O_4S\cdot HCl$	38.23	38.52	5.35	5.44	11.34	11.33
77	CH_3SO_2NH	HO	H	CH_3	37	48	A–C	211.5–212 dec	$C_{10}H_{16}N_2O_4S\cdot HCl$	40.47	40.76	5.78	5.95	10.80	10.76
78	CH_3SO_2NH	HO	H	$(CH_3)_2CH$	38	74	A–C	211.5–212.5 dec	$C_{12}H_{20}N_2O_4S\cdot HCl$	44.37	44.51	6.52	6.25	9.87	9.98
79	CH_3SO_2NH	HO	H	$C_6H_5CH_2CH_2$	39	61	A–C	224–224.5 dec	$C_{17}H_{22}N_2O_4S\cdot HCl$	52.77	52.90	5.99	6.06	8.29	8.19
80	CH_3SO_2NH	HO	H	4-$CH_3OC_6H_4CH_2CH_2$	40	67	B	207.5–208.5	$C_{18}H_{24}N_2O_5S\cdot HCl$	51.85	51.64	6.04	6.18	7.69	7.57

[a] *erythro*. [b] *threo*. [c] One of the two *erythro* racemates. [d] NH_2 = piperidino. [e] Yield from **1**. A 48% yield from **2**. [f] Yield from **35**. A 23% yield from **36**. [g] A, methanol; B, ethanol; C, isopropyl ether; D, ethyl acetate; E, 2-propanol; F, acetonitrile; G, aqueous acetic acid. [h] Hemihydrate.

SCHEME III



When an alcoholic solution of methyl 3-hydroxy-4-nitrobenzoate (IX) was allowed to react with benzyl chloride in the presence of anhydrous potassium carbonate, both benzylation of the phenolic hydroxyl group and hydrolysis of the ester occurred to afford 3-benzyloxy-4-nitrobenzoic acid (X). The acid chloride (XI), prepared by the action of PCl_5 on the acid, was treated with diethyl ethoxymagnesium malonate.[9] The resulting benzoylmalonate was hydrolyzed and decarboxylated with sulfuric acid to yield 3′-benzyloxy-4′-nitroacetophenone (II).

Stereochemistry.—All compounds reported in this work are optically inactive and may consist of one or more racemic modifications. For all those compounds listed in Table III where R equals methyl or ethyl, reduction of the corresponding carbonyl precursors introduces an additional asymmetric center into the molecule. Thus, two racemic modifications of the ephedrine-ψ-ephedrine type are possible. In support of our previous observations,[3] hydrogenolysis of the benzyl groups proceeds appreciably faster than reduction of the carbonyl group. Therefore, reduction of the tertiary aminophenones (VI) bearing a benzyl group on the aliphatic amino nitrogen atom is equivalent to reduction of the debenzylated secondary aminophenone. Reduction of this type of aminophenone yields exclusively the *erythro* racemate.[3,10] Spin-spin coupling constants for the hydrogen–hydrogen interaction on the two adjacent asymmetric centers of these reduction products were all in the order of 3–4 cps.[3,11]

In those instances where a third center of asymmetry in the phenethanolamine (I) is located in the substituent group on the aliphatic nitrogen atom, and R equals methyl or ethyl, four racemates are possible. Two of these are *erythro* and two are *threo*. During larger scale preparation of **72**, it was possible to isolate a second racemate, **73**. Nmr studies indicated that both these racemates were of the *erythro* configuration.

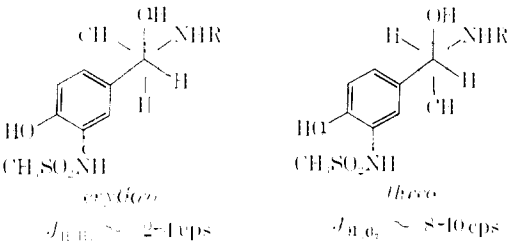
Catalytic hydrogenation of tertiary aminophenones (VI), not containing an amino nitrogen substituent labile to hydrogenolysis, leads to a mixture of the *erythro* and *threo* racemates. Compound **75** was isolated as a mixture, 80% *erythro* ($J_{H_1H_2}$ = 2.4 cps) and 20% *threo* ($J_{H_1H_2}$ = 10.0 cps).

(9) M. Julia and F. Chastrette, *Bull. Soc. Chim. France*, 2255 (1962); G. A. Reynolds and C. H. Hauser, *Org. Syn.*, **30**, 70 (1950).

(10) J. VanDijk and H. D. Mood, *Rec. Trav. Chim.*, **78**, 22 (1959); **80**, 573 (1961).

(11) J. D. Hyne, *Can. J. Chem.*, **39**, 2563 (1961).

Borohydride reduction of a secondary amino ketone **25** gave a mixture of the two possible racemates. These racemates were separated: **64**, *erythro* ($J_{H_1H_2}$ = 3.5 cps); **65**, *threo* ($J_{H_1H_2}$ = 9.4 cps).



In **69** and **70**, there are also two asymmetric centers, but not of the *erythro–threo* type. The stereochemistry of these is not known.

Experimental Section[12]

4′-Acetyl-2′-nitromethanesulfonanilide.—To a stirred solution of 400 ml of red fuming nitric acid and 200 ml of glacial acetic acid was added portionwise 74.0 g (0.35 mole) of 4′-acetylmethanesulfonanilide[3] while maintaining a reaction temperature of −6 to −8°. After stirring for 40 min at this temperature, the mixture was poured into 2.5 l. of ice and the resulting solid collected; yield 97.5 g, mp 146–149°. Crystallization from ethyl acetate provided 72.0 g (80%) of product, mp 147.5–150°.

Anal. Calcd for $C_9H_{10}N_2O_5S$: C, 41.85; H, 3.90; N, 10.85. Found: C, 41.60; H, 3.89; N, 11.04.

4′-Acetyl-2′-aminomethanesulfonanilide Hydrochloride (VII). A stirred mixture of 10.3 g (0.04 mole) of 4′-acetyl-2′-nitromethanesulfonanilide and 0.2 g of PtO_2 in 500 ml of methanol was subjected to a hydrogen pressure of 0.21 kg/cm² for 3 hr. The catalyst was removed by filtration and the filtrate was acidified with ethanolic HCl and then concentrated at reduced pressure. Trituration of the residue with 2-propanol gave 7.4 g (70%) of VII, mp 185–189°. Crystallization from methanol–ethyl acetate returned 6.5 g (61%), mp 196–200°.

Anal. Calcd for $C_9H_{12}N_2O_3S \cdot HCl$: N, 10.58; S, 12.12. Found: N, 10.26; S, 11.40.

5-Acetyl-1-methanesulfonylbenztriazole (VIII).—An ice-cold solution of 6.4 g (0.024 mole) of 4′-acetyl-2′-aminomethanesulfonanilide hydrochloride in 20 ml of aqueous 1 *N* HCl was treated with 1.8 g (0.026 mole) of $NaNO_2$ in 5 ml of water. Cooling was removed and the stirred reaction solution was allowed to come to room temperature. After stirring for an additional hour at 40°, the reaction mixture was diluted with 100 ml of water and made alkaline with 1 *N* NaOH. The separated solid was collected, washed with water, dried, and crystallized from methanol–2-propanol, yield 3.7 g (65%), mp 165–167°.

Anal. Calcd for $C_9H_9N_3O_3S$: N, 17.56; S, 13.40. Found: N, 17.57; S, 13.35.

Benzyloxynitrophenones (II). Procedure 1A. 4′-Benzyloxy-3′-nitroacetophenone.—A mixture of 36.2 g (0.2 mole) of 4′-hydroxy-3′-nitroacetophenone,[5] 28.0 g (0.2 mole) of benzyl chloride, 22.0 ml of 50% aqueous KOH solution, 2.0 g of NaI, 200 ml of water, and 300 ml of 95% ethanol was stirred and refluxed for 48 hr. The ethanol was removed at reduced pressure, the cooled aqueous residue was filtered, and the solid was washed with water; yield 43.2 g (80%), mp 110–120°. Crystallization was effected from a butanone–isopropyl ether mixture; mp 135.5–137°.

Procedure 1B. 3′-Benzyloxy-4′-nitroacetophenone.—A mixture of 19.7 g (0.10 mole) of methyl 3-hydroxy-4-nitrobenzoate, 14.0 g (0.11 mole) of benzyl chloride, 17.2 g (0.12 mole) of anhydrous K_2CO_3, and 1.5 g of NaI in 100 ml of 95% ethanol was stirred and refluxed for 48 hr. The cooled mixture was diluted with 1 l. of water and acidified and the precipitate was collected and crystallized from 2-propanol; yield 20.7 g (76%) of 3-benzyloxy-4-nitrobenzoic acid, mp 210–212°.

Anal. Calcd for $C_{14}H_{11}NO_5$: C, 61.54; H, 4.06; N, 5.13. Found: C, 61.43; H, 4.23; N, 5.04.

(12) Corrected melting points were determined with a Thomas–Hoover Unimelt capillary melting point apparatus.

A mixture of 2.7 g (0.01 mole) of the 3-benzyloxy-4-nitrobenzoic acid and 2.0 g (0.01 mole) of PCl_5 was heated on a steam bath until HCl evolution ceased. The mixture was diluted with 50 ml of CCl_4 and filtered, and the residue from the concentrated filtrate was crystallized from heptane; yield 2.5 g (85%) of 3-benzyloxy-4-nitrobenzoyl chloride, mp 96–100°.

Anal. Calcd for $C_{14}H_{10}ClNO_4$: C, 57.65; H, 3.46; N, 4.80; Cl, 12.15. Found: C, 57.53; H, 3.48; N, 4.91; Cl, 12.07.

3-Benzyloxy-4-nitrobenzoyl chloride (29.2 g, 0.1 mole) was treated with diethyl ethoxymagnesium malonate (prepared from 0.11 g-atom of Mg and 0.11 mole of diethyl malonate) according to the manner described by Reynolds and Hauser,[9] providing 16.8 g (62%) of 3′-benzyloxy-4′-nitroacetophenone, mp 90–97°. Crystallization was effected from isopropyl ether, mp 96.5–98.5°.

Aminobenzyloxyphenones (III). Procedure 2A. 4′-Amino-3′-benzyloxyacetophenone.—A sample of 6.7 g (0.025 mole) of 3′-benzyloxy-4′-nitroacetophenone in 200 ml of methanol was reduced in a Parr hydrogenator with 0.2 g of PtO_2 as catalyst. After removal of the catalyst and evaporation of the solvent, the residue was triturated with cold 2-propanol and the solid was collected; yield 4.2 g (70%), mp 72–80°. Crystallization was effected from 2-propanol; yield 3.9 g (65%), mp 79–81°.

Procedure 2B. 3′-Amino-4′-benzyloxybutyrophenone.—A slurry of 56.5 g (0.189 mole) of 4′-benzyloxy-4′-nitrobutyrophenone in 700 ml of absolute ethanol was refluxed with stirring. To this hot solution was first added 5 teaspoons of Raney nickel, and then a solution of 28.4 g (0.566 mole) of 99% hydrazine hydrate in 30 ml of ethanol was added dropwise over 20 min. The mixture was refluxed an additional hour, then filtered through Celite. The filtrate was concentrated at reduced pressure and the residue was triturated with cold 2-propanol and filtered; yield 45.1 g (89%), mp 83–85°. A crystallization from isopropyl ether yielded 40.0 g (79%), mp 84–86°.

Acylbenzyloxyalkanesulfonanilides (IV). Procedure 3A. 5′-Acetyl-2′-hydroxybutanesulfonanilide.—Butanesulfonyl chloride (56.2 g, 0.30 mole) was added dropwise with stirring to a cooled solution of 3′-amino-4′-hydroxyacetophenone hydrochloride (47.0 g, 0.30 mole) in 375 ml of pyridine. After stirring for 2 hr at 25°, the solution was poured into 2.5 l. of ice water. The precipitate was collected and washed successively with water, dilute HCl, and water. The moist solid was dissolved in 2 l. of 0.5 *N* NaOH, and the filtrate was acidified with 6 *N* HCl. The white solid was collected, washed with water, and air dried; yield 64 g (79%), mp 148–154°. Crystallization from 2-propanol yielded 55.0 g (68%), mp 156.5–158.5°.

5′-Acetyl-2′-benzyloxymethanesulfonanilide.—Methanesulfonyl chloride (4.4 g, 0.039 mole) was added dropwise to a stirred mixture of 10.7 g (0.039 mole) of 3′-amino-4′-benzyloxyacetophenone hydrochloride in 50 ml of pyridine. After stirring for 4 hr at room temperature, the solution was poured into 500 ml of ice water and the solid was collected by filtration; yield 10.6 g (97%) of the 5′-acetyl-2′-benzyloxymethanesulfonanilide 3′-amino-4′-benzyloxyacetophenone salt, mp 109–111°. Crystallization from 2-propanol yielded 10.2 g of the salt, melting point unchanged.

Anal. Calcd for $C_{16}H_{17}NO_4S \cdot C_{15}H_{15}NO_2$: C, 66.41; H, 5.75; N, 5.00; S, 5.72. Found: C, 66.99; H, 5.85; N, 5.38; S, 5.19.

The salt (10.2 g) was stirred with 50 ml of 10% NaOH solution, the insoluble material was filtered, washed with water, and dried; yield 5.0 g, mp 124–128°. Recrystallization from 2-propanol gave the purified starting aniline derivative, mp 127–129°. A mixture melting point of this substance with 3′-amino-4′-benzyloxyacetophenone was not depressed, and the infrared spectra of the two were identical.

Acidification of the alkaline filtrate with HCl yielded 5.0 g of solid, mp 140–142°. Crystallization from 2-propanol yielded 4.8 g (75% based on recovered starting material) of anilide product, mp 141.5–142.5°.

Procedure 3B. 4′-Acetyl-2′-benzyloxymethanesulfonanilide.—A solution of 5.6 g (0.049 mole) of methanesulfonyl chloride in 40 ml of benzene was added dropwise to a stirring solution of 11.7 g (0.049 mole) of 4′-amino-3′-benzyloxyacetophenone and 9.8 g (0.098 mole) of triethylamine in 160 ml of benzene. After stirring for 4 hr at 25°, the precipitate was collected, washed with benzene, and then triturated with 300 ml of water; yield 6.0 g, mp 143–147°. An additional 2.5 g of product, mp 143–147°, was obtained by acidifying a 10% NaOH extract of the benzene filtrate; total yield 8.5 g (55%). Crystallization was effected from 2-propanol, mp 146.5–147.5°.

An alkali-insoluble material was isolated in addition to the desired product; mp 176–177.5°, after crystallization from 2-propanol. Elemental analyses indicated this to be the dimesylated product, 4′-acetyl-2′-benzyloxydimethanesulfonanilide.

Anal. Calcd for $C_{17}H_{19}NO_6S_2$: C, 51.37; H, 4.82; N, 3.53; S, 16.13. Found: C, 51.28; H, 4.92; N, 4.02; S, 15.92.

Benzyloxybromoacylalkanesulfonanilides (V). Procedure 4. 2′-Benzyloxy-5′-(2-bromobutyryl)methanesulfonanilide.—A solution of bromine (22.2 g, 0.139 mole) in 100 ml of $CHCl_3$ was added dropwise to a stirred solution of 48.1 g (0.139 mole) of 2′-benzyloxy-5′-butyrylmethanesulfonanilide and 0.2 g of dibenzoyl peroxide in 650 ml of $CHCl_3$. After stirring for 30 min at room temperature, the mixture was washed with water, then saturated $NaHCO_3$ and again with water. The $CHCl_3$ solution was dried ($MgSO_4$) and concentrated at reduced pressure. The residue was taken into 2-propanol and scratched to induce crystallization, and the solid was collected; yield 55.8 g (94%), mp 93–96°. Recrystallization from 2-propanol allowed recovery of 50.5 g (85%), mp 95.5–97.5°.

Aminoacylbenzyloxyalkanesulfonanilides (VI) (Table II). 5′-(2-Benzylmethylaminopropionyl)-2′-benzyloxymethanesulfonanilide (7).—Solid 2′-benzyloxy-5′-(2-bromopropionyl)methanesulfonanilide (8.2 g, 0.02 mole) was added to a stirred solution of 5.0 g (0.041 mole) of benzylmethylamine in 75 ml of acetonitrile, and the mixture was stirred at room temperature for 3 hr. The mixture was concentrated at reduced pressure, the residue was stirred in 300 ml of anhydrous ether and the benzylmethylamine hydrobromide was removed by filtration. The ethereal solution was evaporated, the residue was triturated with isopropyl ether, and the solid was collected by filtration; yield 7.5 g (83%), mp 117–121°. Crystallization from 2-propanol allowed recovery of 5.3 g (59%), mp 119–121°.

2′-Benzyloxy-5′-(2-isopropylaminoacetyl)butanesulfonanilide Hydrochloride (13).—A mixture of 8.8 g (0.02 mole) of 2′-benzyloxy-5′-(2-bromoacetyl)butanesulfonanilide and 2.4 g (0.04 mole) of isopropylamine in 50 ml of acetonitrile was stirred at room temperature for 30 min. The solution was diluted with 300 ml of anhydrous ether and the isopropylamine hydrobromide was removed by filtration. The ethereal filtrate was acidified with ethanolic HCl, the supernatant solution was decanted, and the residue was triturated with 2-propanol. The solid was collected by filtration; yield 4.7 g (52%), mp 165–175°. Crystallization from 2-propanol and then from acetonitrile–isopropyl ether allowed recovery of 4.3 g (47%), mp 173.5–176.5°.

2′-Benzyloxy-5′-[2-(diphenylmethylamino)butyryl]methanesulfonanilide Hydrochloride (4).—To a solution of 3.7 g (0.02 mole) of diphenylmethylamine in 25 ml of acetonitrile was added 4.3 g (0.01 mole) of 2′-benzyloxy-5′-(2-bromobutyryl)methanesulfonanilide. The mixture was refluxed for 24 hr and then chilled, 200 ml of anhydrous ether was added, and the diphenylmethylamine hydrobromide was removed by filtration. The ethereal filtrate was acidified with ethanolic HCl, and the separated solid was collected by filtration; yield 5.0 g (88%), mp 179–181°. Crystallization from acetonitrile–isopropyl ether yielded 4.5 g (79%), mp 186.5–188.5°.

4′-(2-Aminoacetyl)-2′-benzyloxymethanesulfonanilide Hydrochloride (35).—A solution of 8.0 g (0.02 mole) of 2′-benzyloxy-4′-(2-bromoacetyl)methanesulfonanilide and 4.2 g (0.03 mole) of hexamethylenetetramine in 150 ml of $CHCl_3$ was stirred at room temperature for 3 hr. The accumulated precipitate was collected by filtration and washed with $CHCl_3$ and then acetone; yield 7.2 g (66%), mp 157–160°. The quaternary complex was hydrolyzed by heating with 50 ml of 95% ethanol and 8 ml of concentrated HCl until solution was affected. On cooling, the amino ketone hydrochloride crystallized and was collected by filtration. The solid was triturated with 15 ml of cold water, filtered, and dried at reduced pressure; yield 4.4 g (59% over-all), mp 196.5–198°.

Hydroxyalkanesulfonamidophenethanolamines (I) (Table III). 2′-Hydroxy-5′-[1-hydroxy-2-(isopropylamino)ethyl]butanesulfonanilide hydrochloride (52).—A solution of 4.3 g (0.0094 mole) of 2′-benzyloxy-4′-(2-isopropylaminoacetyl)butanesulfonanilide hydrochloride (**13**) in 100 ml of 90% ethanol with 0.5 g of 10% Pd–C was subjected to 3.5 kg/cm² hydrogen pressure in a Parr hydrogenator. Consumption of the calculated quantity of hydrogen was complete after shaking the mixture at room temperature for 4 hr. After removal of the catalyst and evaporation of the solvent, the oily residue was triturated with 50 ml of cold 2-propanol to obtain a slurry of a white solid. After dilution with 50 ml of isopropyl ether, the solid was collected by filtration;

TABLE IV

ADRENERGIC AND BLOOD PRESSURE EFFECTS OF ALKANESULFONAMIDOHYDROXYPHENETHANOLAMINES[a]

	Adrenergic potency						Adrenergic specificity				
	α		β								
No.	Stimulant[b] (seminal vesicle)	Blockade[c] (seminal vesicle)	Stimulant[d] (rat uterus)	Stimulant[e] (trachea)	Blood pressure potency Pressor[f]	Depressor[g]	SV U[h]	SV/T[i]	T/D[k]	T/D[l]	T/T[m]
41	7.8		0.003	0.005	2.0		2.6	31			1.7
42	1.9		0.002	0.001	1.0		1.0	38			0.5
43	0.2		0.01	0.01	0.1		0.02	0.4			1.0
44	0.7		0.0003	0.002	0.2		2.3	7			6.7
45	12		0.001	0.03	1.0		12	8			30
46	1.0		0.005	0.02	0.2		0.2	1.0			4.0
47	0.004		0.01	0.2	0.001		0.0004	0.0004			20
48	0.7		0.0001	0.003	0.005		7	5			30
49	0.01		1.2	1.0		0.2	0.000008	0.0002	6	5	0.8
50		0.0001	0.1	0.006		0.005			20	1.2	0.06
51		0.00007	0.1	0.5		0.01			10	70	7.0
52		0.0001	0.02	0.03		0.002			10	15	1.5
53		0.0001	0.2	1.4		0.05			4	28	7.0
54		<0.0001	0.02	0.02		0.002[j]			10	10	1.0
55		0.003	0.5	0.3		0.002			250	150	0.6
56		0.004	0.3	0.4		0.01			30	40	1.3
57		0.001	0.06	0.2		0.0005			120	400	3.3
58		0.003	0.07	0.03		0.001			70	30	0.4
59		0.01	0.1	0.4		0.002			50	200	4.0
60		0.004	0.2	0.6		0.01			20	60	3.0
61		0.0008	0.3	3.0		0.01			30	300	10
62		0.001	0.003	0.01		0.002			1.5	5	3.3
63		0.0003	0.07	0.1		0.002[j]			35	50	1.4
64		0.005	0.0002	0.0003		0.0001			2	3	1.5
65		0.004	0.00002	<0.001		0.0001			0.2		
66		<0.0001	0.06	0.1	0.01						1.7
67		0.002	0.002	0.02		0.0002[j]			10	100	10
68		0.004	0.1	0.06		0.01			10	6	0.6
69		0.006	0.4	0.8		0.01[k]			40	80	2.0
70		0.04	4.0	4.0		0.3			13	13	1.0
71		0.005	0.04	0.04		0.0002			200	200	1.0
72		0.15	0.06	0.5		0.01			6	50	8.3
73		0.01	0.04	0.5		0.002			20	250	12
74		0.0008	0.02	1.0		0.005			4	200	50
75		0.0005	0.00003	<0.0001		0.00002			1.5		
76	<0.00001	<0.000001	0.00001	<0.0001		<0.00001					
77	<0.00001	<0.000001	<0.000001	<0.0001		<0.00001					
78		<0.000001	<0.000001	<0.0001		<0.00001					
79		0.0002	<0.000001	<0.0001		<0.00001					
80		0.0001	<0.000001	<0.0001		0.00005					
Norepinephrine	1.0		0.001	0.02	1.0		1.0	1.0			20
Epinephrine	3.3		0.2	0.15	2.0		0.02	0.4			0.8
Isoproterenol			1.0	1.0		1.0			1.0	1.0	1.0
Phentolamine		1.0									

[a] The pharmacological data has been calculated on the basis of the sulfonamidophenethanolamine bases. For a description of the test methods see ref 13. [b] Relative potency for producing contractions of the rat seminal vesicle 50% as intense as those produced by 2.0 μg/ml of *l*-epinephrine (0.9 μg/ml of norepinephrine = 1). [c] Relative potency for reducing by 50% the contraction of the rat seminal vesicle induced by 4.0 μg/ml of *l*-norepinephrine (0.015 μg/ml of phentolamine = 1). [d] Relative potency for reducing by 50% the spontaneous contractions of the rat uterus (0.03–0.08 ng/ml of isoproterenol = 1). [e] Relative potency for relaxing by 75% the spontaneous tonus of the guinea pig tracheal spiral (4 ng/ml of isoproterenol = 1). [f] Relative potency for producing a 15–25% increase in mean arterial blood pressure of the anesthetized dog (1 μg/kg of norepinephrine = 1). [g] Relative potency for producing a 15–25% decrease in mean arterial blood pressure of the anesthetized dog (0.1 μg/kg of isoproterenol = 1). [h] Pressor at higher doses. [i] Ratio of α-mimetic (seminal vesicle) to β-mimetic (rat uterus) potencies, norepinephrine = 1. [j] Ratio of α-mimetic (seminal vesicle) to β-mimetic (guinea pig trachea) potencies, norepinephrine = 1. [k] Ratio of β-mimetic (rat uterus) to depressor potency, isoproterenol = 1. [l] Ratio of β-mimetic (guinea pig trachea) to depressor potency, isoproterenol = 1. [m] Ratio of guinea pig trachea potency to rat uterine potency, isoproterenol = 1.

yield 3.15 g (91%), mp 145.5–148°. Crystallization from ethanol–isopropyl ether yielded 2.6 g (75%), mp 150–151.5°.

2′-Benzyloxy-5′-[2-(4-chlorophenethylamino)-1-hydroxypropyl]methanesulfonanilide Hydrochloride (64 and 65).—A solution of 8.5 g (0.016 mole) of 2′-benzyloxy-5′-[2-(4-chlorophenethylamino)-2-propionyl]methanesulfonanilide hydrochloride (**25**) in 100 ml of methanol was treated with 32 ml (0.032 mole) of of 1.0 *N* NaOH solution. To this mixture was added 0.61 g (0.016 mole) of $NaBH_4$ and stirring was continued for 1 hr at room temperature. The mixture was concentrated at reduced pressure, the solid residue was slurried in 50 ml of methanol and filtered, and the filtrate was acidified with ethanolic HCl. This acidic solution was evaporated at reduced pressure and the residue was triturated in 50 ml of 2-propanol. The separated solid was collected by filtration, 5.5 g (65%), mp 206–208°. After crystallization from methanol–ethanol (1:1), 2.7 g of solid was collected, mp 208.5–210°, shown by nmr to be the *erythro* racemate (**64**). By concentration of the methanol–ethanol filtrate, a second crop of solid was collected, 2.4 g, mp 177–180°. This second product was crystallized from acetonitrile to yield 2.0 g,

mp 178–180°, and demonstrated by nmr to be the *threo* racemate (**65**).

Structure–Activity Relationship

The concept of dual adrenergic receptors, as proposed by Ahlquist,[13] is employed in the following discussion to delineate sympathomimetic action. Primary screening was designed to reveal β-receptor stimulation and blockade and α-receptor stimulation and blockade. For these purposes, relaxation of the uterine horn from diestrus rats and relaxation of the guinea pig tracheal spiral were used as initial *in vitro* tests for β-receptor activation. β-Receptor blockade was measured by the antagonistic action of the compounds toward isoproterenol relaxation of the isolated guinea pig tracheal spiral. Potent α-receptor activation was revealed by examination of the spasmogenic action of the compounds on the isolated, quiescent rat seminal vesicle. α-Receptor blockade 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.

A summary of the pharmacologic effects of the (1-hydroxy-2-aminoalkyl)hydroxyalkanesulfonanilides is found in Table IV. Except for the blood pressure effects, the values listed are interpolated from dose–response curves at two–four concentrations of two–five trials each. The test procedures are conventional and have been described in previous reports from this laboratory.[3,14] All potencies are given as multiples of either norepinephrine, isoproterenol, or phentolamine. The various ratios listed in Table IV represent an attempt to outline the specificity of action in relation to an α-adrenergic standard, norepinephrine, and a β-adrenergic standard, isoproterenol.

The discussion is organized around structural changes and their effect on activity, with no attempt to detail each and every compound.

(1) Members of the *meta* series are α- and β-receptor agonists, reversible α-receptor blockers, and relatively ineffective β-receptor blocking agents. Compounds of the *para* series, **76–80**, are much less active in all respects.

(2) Small groups on the amino nitrogen, such as hydrogen and methyl, favor α-adrenergic agonist actions and pressor responses. On the basis of the *in vitro* tests, compounds **41** and **45** would appear to be more potent than epinephrine as α-adrenergic agents, and **42**, **44**, **46**, and **48** are approximately equipotent to norepinephrine. Compounds **41**, **42**, **44**, **45**, and **48** exhibit a greater specificity toward α-adrenergic activation than does norepinephrine. Proof for adrenergic innervation by this group of compounds is the fact that the α-adrenergic blocking agents, phentolamine or phenoxybenzamine, blocked the spasmogenic action of **43–45** and **49** on the rat seminal vesicle and the *in vivo* pressor responses of **43–45** in the dog. In addition, the *in vitro* β-adrenergic action of **43–45** was blocked by the β-adrenergic blocking agent, sotalol.[15]

(3) Substitution of isopropyl or larger groups on the side-chain nitrogen atom gives rise to a series of compounds with β-adrenergic actions, as measured by the *in vitro* tests and their general depressor responses in the dog. Proof for the adrenergic nature of these actions is the fact that the relaxant action of **49**, **51–53**, **57**, **58**, **60**, **62–64**, **67**, **69–71**, **73**, and **74** on the guinea pig tracheal spiral and **60** and **78** on the rat uterus were blocked by the β-adrenergic blocking agent, sotalol.[15] In addition, the depressor and chronotropic responses of **49**, **51–53**, **57**, **58**, **60**, **62–64**, **67**, **69–71**, **73**, and **74** are also reversibly and largely blocked by the β-adrenergic blocking agent, sotalol. Such results are evidence that the principal action of these compounds involves adrenergic innervation. We recognize, of course, that many aralkylamines, such as **57–74**, exhibit a small nonadrenergic relaxant component as part of their pharmacologic profile.[16] When compounds such as **60** and **72** were continuously infused into anesthetized intact dogs, pretreatment with the β-adrenergic blocking agent, sotalol,[3,15] failed to antagonize completely their blood pressure lowering actions. That this action is papaverine-like, rather than α blocking, is reflected in the differences in α-blocking action for these two compounds.

Compound **49** demonstrates the same general potency and specificity of action as does isoproterenol, to which it is related structurally. Compound **49** does, however, have weak α-adrenergic stimulant action and also a longer duration of action than isoproterenol, when examined *in vivo*. Among the several phenethyl and substituted phenethyl structures, **55–67**, many are potent β-adrenergic stimulants. Exceptions to this are **64** and **65**, which have the *para* phenolic hydroxyl group masked as a benzyl ether. Compound **66**, although active as a β-adrenergic agonist in the isolated tests, exhibits only pressor responses in the intact dog. The depressor component of **66**, not discernible by changes in dosage, was, however, revealed by pretreatment with the α-adrenergic blocker, phenoxybenzamine. Several compounds of this group exhibit a biphasic depressor–pressor response, dependent upon dose. Compounds **68–71** bear an arylisopropyl substituent on the amino nitrogen atom. These can be considered γ-methyl derivatives of the phenethyl structures.[17] It appears that the introduction of the γ-methyl is not inimical to β-stimulant actions.

Compound **75**, wherein the amino nitrogen is tertiary and part of a piperidine ring, departs radically in action from the secondary amines. It is a very weak

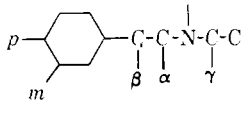
(13) R. P. Ahlquist, *Am. J. Physiol.*, **153**, 586 (1848).

(14) P. M. Lish, K. W. Dungan, and E. L. Peters, *J. Pharmacol. Exptl. Therap.*, **129**, 191 (1960); K. W. Dungan and P. M. Lish, *J. Allergy*, **32**, 139 (1961).

(15) This compound, 4′-[2-(isopropylamino)-1-hydroxyethyl]methanesulfonanilide,[3] has also been identified as MJ-1999 in the scientific literature.

(16) B. B. Clark, P. M. Lish, and K. W. Dungan, Proceedings of the First International Pharmacological Meeting, Stockholm, Sweden, 1961, Vol. 7, K. J. Brunings, Ed., Pergamon Press, Oxford, England, 1963, p 291.

(17) In this respect, the isopropyl group can be considered the γ-methyl homolog of ethyl norepinephrine and the *t*-butyl substituent as the γ,γ-dimethyl derivative. The designations of the carbon atoms in phenethyl and phenethanolamines is at best chaotic. The following is a guide.



β-receptor-like agonist, and its depressor actions are not blocked by sotalol.

(4) Replacement of one of the hydrogens on the α-carbon by methyl or ethyl results in a decrease of α-adrenergic action. The incremental decrease from α-methyl to α-ethyl is greater than from α-hydrogen to α-methyl. These changes also reduce α-adrenergic specificity. With the β-adrenergic agonists, α-carbon substitution tends to decrease activity. Substitution by α-ethyl would appear disproportionately to favor retention of bronchodilator potency, in accord with the observations of Lands.[18,19] Compound **66**, which exhibited a pressor response, is converted to a depressor substance by α- or γ-methyl substitution with **69**, the γ-methyl derivative, demonstrating greater *in vitro* β-agonist potency than **67**, the α-methyl derivative.

(5) Replacement of the methanesulfonamido (MSA) group by butanesulfonamido (BSA) would appear to result in general over-all retention of specificity with reduction of potency. It does appear, however, that bronchodilation, as measured by relaxation of the tracheal spiral, is preferentially retained or enhanced in relation to actions of the corresponding MSA compounds.

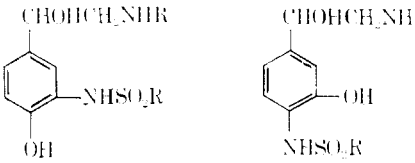
(6) Reversible α-adrenergic blocking action is found among the β agonists. Activity, approximately 25% of phentolamine, is demonstrated by **72**. Interestingly, **73** which differs from **72** in being the other *erythro* racemate, is appreciably less active as an α antagonist. The structure–activity relationships are not very clear for this type of action; yet, it would appear that rather large groups substituted on the amino nitrogen are essential.

Other biological information relevant to 2′-hydroxy-5′-(1-hydroxy-2-isopropylaminoethyl)methanesulfonanilide (**49**),[20] has been reported.[21,22] This compound is currently undergoing clinical investigation as a bronchodilator. Additional biological data have been published for 2′-hydroxy-5′-[1-hydroxy-2-(4-methoxyphenethylamino)propyl]methanesulfonanilide (**60**),[20,22] and 2′-hydroxy-5′-[1-hydroxy-2-(1-phenoxy-2-propylamino)propyl]methanesulfonanilide (**72**),[20,22,23] which are being investigated clinically as uterine relaxants.[24] Further biological data has also been published on the α-adrenergic agonist, 2′-hydroxy-5′-(1-hydroxy-2-methylaminoethyl)methanesulfonanilide (**45**).[20,22]

Discussion

By virtue of its steric and acidic properties, the alkanesulfonamido group, properly positioned, is considered to be capable of interacting with an adrenergic receptor in a manner analogous to the phenolic hydroxyl group.[2,3] Introduction of both an alkanesulfonamide and a hydroxy group into the *meta* and *para* positions of the benzene ring of otherwise suitably substituted phenethanolamines should result in compounds capable of adrenergic activations approximating even more closely those of the catecholamines, norepinephrine, epinephrine, and isoproterenol. On the basis of our biological test results, this hypothesis has been partially validated.

It is interesting, however, to note the difference in the pharmacological potencies of comparable compounds in the *meta* and *para* series. Whereas compounds of the *meta* series efficiently subserve α- and β-adrenergic events, similarly constituted molecules of the *para* series are considerably less active. This difference of pharmacological activity of the two series resulting from the simple transposition of the methanesulfonamide and phenolic hydroxyl groups was rather unexpected.



meta series *para* series

The following observations would seem to pertain to this situation. Mono-*m*-alkanesulfonamidophenethanolamines and the mono-*m*-hydroxyphenethanolamines elicit in fair measure the direct sympathomimetic actions of the catecholamines.[3,25] These pharmacodynamic effects are, of course, influenced by the nature of the substituent on the side-chain amine nitrogen atom. The mono-*p*-methanesulfonamidophenethanolamines display β-adrenergic blocking effects as their principal biological action.[3,26] The mono-*p*-hydroxyphenethanolamines are more difficult to characterize. With small substituents on the side-chain amine function, relatively feeble α-adrenergic stimulant action can be demonstrated;[25] with larger substituents, β-adrenergic agonist action is demonstrable.[27]

With the mixed catechols reported here, the substitutions can be examined from two viewpoints. (1) Addition of an alkanesulfonamide group to the *meta* position of a *p*-hydroxyphenethanolamine results in the establishment of classical potent sympathomimetic actions. Stated conversely, the incorporation of a hydroxyl group into the *para* position of a *m*-alkanesulfonamidophenethanolamine results in an enhancement of existing significant sympathomimetic action. (2) Addition of a methanesulfonamide group to the *para* position of a *m*-hydroxyphenethanolamine reduces the inherent sympathomimetic action of this class of compounds. Stated conversely, incorporation of a hydroxyl group into the *meta* position of a *p*-methanesulfonamidophenethanolamine essentially obliterates the β-receptor blocking action of the latter compounds. In any case, it appears as though the ability of the *para* series to stimulate or block the adrenergic receptor has

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(26) P. M. Lish, J. H. Wakel, and K. W. Dungan, *J. Pharmacol. Exptl. Therap.*, **149**, 161 (1965); H. C. Stanton, T. Kirchgessner, and K. Parmenter, *ibid.*, **149**, 174 (1965); K. C. Kwan, D. A. Riggilo, and P. M. Lish, *ibid.*, **149**, 183 (1965).

(27) E. J. Ariëns, M. J. G. A. Wuden, P. F. Sommerijs, and A. M. Simonis, *Arzneimittel-Forsch.*, **13**, 541 (1963).

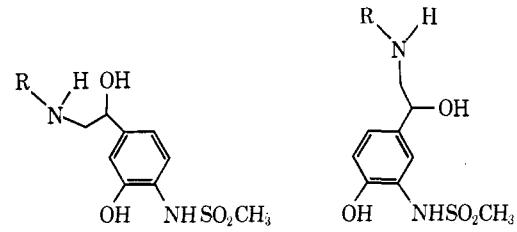
been markedly diminished in relation to the corresponding monosubstituted phenolic or methanesulfonamidophenethanolamines.

At the present time our chemical measurements, solubilities, melting points, partition coefficients, acidities, and spectral data, do not allow for a distinction between the *meta* and *para* series of mixed catechols, which can be interpreted as the same order of magnitude as the difference in pharmacological action. These observations lead us to suggest that the acidic character and placement for the benzene ring substituents in phenethanolamines plays a more significant role than has hitherto been appreciated. Although the literature gives considerable testimony to studies[28] concerning the effect of basicity on the activity of phenethanolamines, the role of the acidic function(s) in the benzene ring has perhaps been too long neglected, due in part to the unavailability of suitable substituent groups, other than the phenolic hydroxyl itself.

On the basis of our preliminary observations,[2,3] it appears that methanesulfonanilide and its ethanolamine derivatives are stronger acids, by about 0.5–1.0 pK_a unit, than phenol and its corresponding ethanolamine derivatives. When both a methanesulfonamide and phenolic hydroxyl group are incorporated, *ortho* to each other, into a phenethanolamine, the first acidic ionization is enhanced by about 0.5 pK_a unit relative to the corresponding monomethanesulfonamido compound. The significant suggestions and observations of Kappe and Armstrong[29] relating to the enhanced acidity (~0.5 pK_a unit) for the first phenolic hydroxyl group and the depressed acidity (3–4 pK_a units) for the second phenolic hydroxyl group of a catecholamine, when compared to a corresponding monophenolic phenethanolamine, evidently carry over to the two series of mixed catechols reported here. In the light of these observations, we suggest that in both series, *meta* and *para*, the alkanesulfonamido group is acting as the prime acidic binding functionality and the phenolic hydroxyl group as a supplementary acidic group.

Therefore, it would appear that the *meta*-positioned phenolic hydroxyl group or its chemical equivalent is a key requisite for full receptor interaction.[25] Other prime points of attachment are, of course, the alcoholic hydroxyl group and the amino nitrogen atom and the benzene ring itself.[25,30]

The reduced adrenergic activity of the mixed catechol series wherein the hydroxyl group is at the *meta* position and the methanesulfonamido group is at the *para* position of the benzene ring can be rationalized on the basis that the more strongly acidic *p*-methanesulfonamido group, rather than the *m*-hydroxyl group, is interacting with a complimentary *meta* receptor functionality. Therefore, supplemental binding by the *m*-hydroxyl group results in a two-point or hinge-type binding with consequent displacement, by 60°, of the ethanolamine side chain, away from those receptor functionalities with which it would ordinarily be considered to interact. This hypothesis is schematically illustrated as follows. The absolute geometry of this situation is such that it makes no difference what the



para series *meta* series

conjectured details and arrangements are for the remainder of the receptor site functionalities. This 60° displacement makes it impossible for the lateral ethanolamine side chain of the *para* series of the mixed catechols to replicate any total disposition for the same side chain in the *meta* mixed catechol and catechol series. In this light, the compounds of the *para* series might be expected to exert a biologic effect approaching that of compounds in which the ethanolamine side chain is entirely absent.[31] Some credence to such a speculation is partially substantiated by reports of the effects of pyrocatechol[32] and tropolone[33] on the adrenergic system. Indeed, 2′-hydroxy-4′-(1-hydroxy-2-isopropylaminoethyl)methanesulfonamide (**78**) exhibits α- and β-antagonist actions more similar to 4-methyl tropolone[33] than it does to the corresponding compound in the *meta* series, **49**, or to isoproterenol.

For the purpose of this explanation, it matters not whether the receptor site is conceived to preexist as such or is induced by the agonist. In the first instance, the total fit is incomplete. With the second, induction is incomplete or the total induced receptor conformation is not responsive to the triggering of highly specific adrenergic actions.

Such an hypothesis can also accommodate the display of sympathomimetic or sympatholytic actions of the monophenolic and monoalkanesulfonamido-*m*- and -*p*-phenethanolamines. In these instances, single-point binding *via* an acidic benzene ring substituent does not preclude approximate total receptor interaction for the mono-*para*-acidic phenethanolamines and rather exact total receptor interaction for the mono-*meta*-acidic phenethanolamines. The bronchodilator, 2-isopropylamino-1-(3,5-dihydroxyphenyl)ethanol,[34] possessing two benzene ring hydroxyl groups, each *meta* to the ethanolamine side chain, evidences sympathomimetic potency approximating more closely that of the mono-*m*-hydroxy analog rather than that of isoproterenol,[25] or **49** of this work.

Unfortunately, a great deal of structure–activity correlations relating to sympathomimetic amines can be faulted on the cumulative effect of several items. The first is biological action of orders of magnitude less than the catecholamines, often complicated by the fact that blood pressure is the biological event being monitored. This is then further complicated by the compounds of such studies lacking sufficient structural similarity to the catecholamines.

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(30) B. Belleau, ref 16, p 75.

(31) B. Belleau and J. Burba, *J. Med. Chem.*, **6**, 755 (1963).

(32) E. S. Johnson, *J. Pharm. Pharmacol.*, **14**, 272 (1962).

(33) M. F. Murnaghan and J. M. Mazurkiewicz, *Rev. Can. Biol.*, **22**, 99 (1963).

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The recent thermodynamic examination of the cholinergic receptors by Belleau[35] gives considerable testimony to the conceptual trap that may develop when the most common drug functionality is used as a basis for depicting drug-receptor molecularity. His suggestion is that many years of study, concerned with simple quaternary salts, has given an inaccurate visualization of the cholinergic receptor, and that it is only possible to generate a precise visualization when potent, structurally pertinent compounds are studied.

The diminished activity of compounds from the *para* series, in relation to corresponding structures from the *meta* series, poses a difficulty in rationalizing these observed facts with current concepts of α- and β-adrenergic activations.[36-38]

From the *meta* series, compounds **41** and **45** possess the small amine moiety in conjunction with a pseudocatechol system, which satisfy, structurally and biologically, α-receptor agonist concepts. Likewise, **49** with a bulkier nitrogen substituent and the pseudocatechol ring system, meets the rather vague, residual definitions for β-receptor agonists.

In contrast, the corresponding compounds from the *para* series, **76–78**, have analogous substitutions on the nitrogen atom, but differ only by encompassing an isomeric pseudo-catechol system. Since we have no evidence, either *in vitro* or *in vivo*, that compounds of the *para* series are altered, destroyed, or transported differently from those of the *meta* series, we can only conclude that they are "bound" differently.

This constrains us to the conclusion that, when present, the catechol structure, or its equivalent, plays a role energetically superior to the amino function. It must then follow, that nonphenolic or monophenolic phenethanolamines can not chemically relate to the same total receptor functionalities as the catecholamines or their equivalents reported here. Hence, great care must be exercised when such partial structures are substrates for catecholamine-receptor theories.

These suggestions cannot be construed to mean that the amine portion of a catecholamine is unimportant. For significant sympathomimetic action, the literature gives considerable silent testimony to the fact that the amine must bear at least one hydrogen atom, other than the one arising from any potential protonation process. In this work, the only tertiary amine reported is **75**, in which the amino nitrogen is part of a piperidine ring. It is somewhat discomforting to rationalize away the relative inactivity of this compound on the basis of rather vague steric effects.

(35) B. Belleau, 152nd National Meeting of American Chemical Society, Division of Medicinal Chemistry, New York, N. Y., Sept 1966, Abstract 38P.

(36) B. Belleau in "Adrenergic Mechanisms," J. R. Vane, C. E. W. Wolstenholme, and M. O'Connor, Ed., Little, Brown and Co., Boston, Mass., 1960, pp 223-244.

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Studies on Latent Derivatives of Aminoethanethiols as Potentially Selective Cytoprotectants. VI. Synthesis of N-(2-Mercaptoethyl)carbamoylamino Acids[1]

EZRA KHEDOURI, VYTAUTAS GRUBLIAUSKAS, AND ORRIE M. FRIEDMAN

Collaborative Research, Inc., Waltham, Massachusetts 02154

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The N-(2-mercaptoethyl)carbamoyl derivatives of a series of amino acids were synthesized by reaction of 2-thiazolidinone with the sodium salts of β-alanine, glycine, L-leucine, L-alanine, L-methionine, and L-aspartic acid. Attempts to prepare the acids by hydrolysis of the corresponding ethyl esters, obtained by condensation of cysteamine with the amino acid ester isocyanates, were unsuccessful and led only to formation of hydantoins. When administered to tumor-bearing rats, the glycine and alanine derivatives released small but significant levels of cysteamine in three tissues. With four others studied, the derivatives of phenylalanine, methionine, aspartic acid, and β-alanine, little or no cysteamine was found in any of the 15 tissues assayed.

The effectiveness of either radiation or alkylating agents in cancer chemotherapy might be increased significantly by delivery of cytoprotectants as 2-mercaptoethylamine[2] selectively to normal tissues most susceptible to damage, particularly intestinal epithelium and bone marrow. Larger doses of nitrogen mustards or radiation than are normally safely tolerated might then be administered.

One possible manner of such selective delivery would be by administration of 2-mercaptoethylamine as a "latent" chemical derivative from which it could be released enzymatically or otherwise at intracellular sites in the critical tissues. This paper describes the synthesis and properties of a series of N-(2-mercaptoethyl)carbamoylamino acids as possible derivatives of cysteamine of this type.

The mercaptoethylcarbamoyl derivative (II) of β-alanine, glycine, L-leucine, L-phenylalanine, L-glutamic acid, L-alanine, L-methionine, and L-aspartic acid were ultimately prepared by an entirely new direct route which consisted of heating a mixture of 2-thiazolidinone[3]

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(2) For a discussion and other references, see S. F. Contractor, *Biochem. Pharmacol.*, **12**, 821 (1963).

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