TABLE I

L-, D-, AND DL-EPHEDRINE PHOSPHATES

Compd	Mp, °C	$[\alpha]^{25}D$, deg (c 2)	Yield, %	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found	P, % Calcd	P, % Found	Cl, % Calcd	Cl, % Found
IIa	90–91[a]	−74.6[c]	67		48.90	49.10	5.34	5.50	5.70	5.74	12.64	12.85	14.43	14.43
IIb	90–91[a]	+75.2[c]	75	$C_{10}H_{13}ClNO_4P$	48.90	48.72	5.34	5.57	5.70	5.58	12.64	12.51	14.43	14.56
IIc	79–80[a]		84		48.90	49.07	5.34	5.26	5.70	5.56	12.64	12.78	14.43	14.58
IIIa	178–179[b]	−48.9[d]	76		42.64	42.88	6.09	6.22	4.98	5.16	11.01	10.96	12.59	12.68
IIIb	178–179[b]	+49.5[d]	90	$C_{10}H_{17}ClNO_4P$	42.64	42.52	6.09	6.01	4.98	5.11	11.01	11.20	12.59	12.73
IIIc	[e]	...	...		...	...	...	...	...	...	...	...	...	...
IVa[g,h]	242–243	−52.1[d]	84		49.02	49.10	6.58	6.80	5.76	5.84	12.66	12.51		
IVb	241–243	+53.3[d]	86	$C_{10}H_{16}NO_4P$	49.02	48.88	6.58	6.44	5.76	5.68	12.66	12.46		
IVc	250–252	...	79[f]		49.02	48.91	6.58	6.73	5.76	5.61	12.66	12.59		

[a] Crystallized from petroleum ether (bp 60–68°). [b] Crystallized from an ethanol–ether mixture. [c] In benzene. [d] In water. [e] Hygroscopic. [f] The reported yield has been referred to the quantity of IIc. [g] Barium salt, mp 192–193°; cyclohexylammonium salt, mp 234°; sodium salt, mp 254°. [h] Ultraviolet spectrum: λ_{max}^{EtOH} 207 mμ (log ε 3.91), 257 mμ (log ε 2.33).

TABLE II

TOXICITY OF EPHEDRINE AND DERIVATIVES

Compd	LD_{50} (mouse), mg/kg Po	Sc	Ip	Iv
Ia·HCl	400	1000	260	120
Ia·HCl[a]	970	790	333	118
IVa	1065	2000	2000	400
IVa[a]	1142	1707	2386	1338
Ib·HCl	785	425	250	175
IVb	1800	865	815	815
Ic·HCl	700	900	260	135
IVc	2000	1150	790	840

[a] Determined on isolated animals.

2-propanol–concentrated NH_4OH–water (20:1:2), and B, chloroform–methanol–glacial acetic acid (1:1:0.1); the time was 2 hr. To detect L-ephedrine, the chromatogram was sprayed with 0.4% ninhydrin in 1-butanol; ephedrine appeared as a mauve spot. To detect L-ephedrine phosphate, the chromatogram was first sprayed with Neatan® (Merck, Darmstadt) and then with a phosphate reagent [70% $HClO_4$–1 *N* HCl–ammonium molybdate (5:10:1) diluted to 100 ml with water]. After heating to 70° and exposure to H_2S, ephedrine phosphate appeared as a blue spot. For L-ephedrine and L-ephedrine phosphate, respectively, the R_f values in solvent A were 0.65 and 0.00 and in solvent B were 0.53 and 0.27.

Pharmacologic evaluation showed that the phosphates IVa–c have a consistently lower toxicity than the corresponding ephedrines (Ia–c).[8] The results are listed in Table II. Tests of the activity of these compounds on the cardiovascular system (cat) did not reveal any significant difference between the various compounds. However, in comparison with Ia, IVa has shown a significantly lower (eightfold) hypertensive activity. The antibronchospastic activity is not improved by phosphorylation.

(8) L. Coscia, G. De Natale, and P. Causa, Communication at the 13th Meeting of Società Italiana di Farmacologia, Palermo, Italy, April 1965.

New Compounds

Piperazinesulfamylurea Hypoglycemic Agents. V.

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Previous publications from these laboratories[1] have demonstrated the hypoglycemic activity associated with a series of sulfamylurea and sulfamylsemicarbazides. This communication deals with the synthesis of a series of sulfamylureas in which the sulfamyl portion of the structure is derived from an acylated piperazine derivative.

The preparation of the final products (Table I) was most conveniently carried out by a previously described method.[1] Acylation of 1-sulfamylpiperazine with the appropriate acylating agent provided a synthetic route to the requisite intermediates. Using reported screening methodology[1] compounds **2** and **5** showed hypoglycemic activity, but of a degree less than the standard, chlorpropamide.

Experimental Section[2]

1-(1-Acetyl-4-piperazinesulfonyl)-3-cyclohexylurea.—A mixture of 3.4 g (0.015 mole) of 4-acetyl-1-sulfamylpiperazine sodium salt[1b] and 4.99 g (0.017 mole) of N,N-diphenyl-N′-cyclohexylurea[1] was heated overnight on a steam bath. The cooled reaction mixture was diluted with 125 ml of water and extracted with three 100-ml portions of ether. The aqueous layer was separated and acidified with 6 *N* HCl. The precipitated solid was filtered and dried *in vacuo* over P_2O_5.

The sulfamylureas were prepared by a similar procedure in yields of 50–65%. The sulfamylureas and their physical properties are listed in Table I.

1-Sulfamyl-4-chloroacetylpiperazine.—To a suspension of 12.2 g (0.075 mole) of 1-sulfamylpiperazine[1b] in 90 ml of methylene chloride was added 18.6 g (0.11 mole) of chloroacetic anhydride in 60 ml of the same solvent. The mixture was allowed to stir for 1 hr and was then filtered, 15.4 g, mp 156–160°. Recrystallization from methanol gave the pure product, 10.8 g, mp 172–173°.

Anal. Calcd for $C_6H_{12}ClN_3O_5S$: C, 29.8; H, 5.0; N, 17.4. Found: C, 29.8; H, 5.1; N, 17.4.

1-Sulfamyl-4-methoxyacetylpiperazine.—Methoxyacetyl chloride (5.9 g, 0.055 mole) was added gradually to a stirred solution of 8.25 g (0.05 mole) of 1-sulfamylpiperazine and 5.5 g (0.055 mole) of triethylamine in 75 ml of dimethylformamide (DMF). The resulting solution was allowed to heat on a steam bath followed by cooling and the addition of ether. The resulting precipitate was filtered and washed with ethanol, 7.8 g, mp 146–151°. Recrystallization from ethanol gave 6.7 g, mp 158–160°.

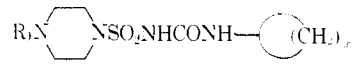
Anal. Calcd for $C_7H_{15}N_3O_4S$: C, 35.4; H, 6.4; N, 17.7. Found: C, 35.1; H, 6.0; N, 17.6.

(1) J. M. McManus, J. W. McFarland, C. F. Gerber, W. M. McLamore, and G. D. Laubach, *J. Med. Chem.*, **8**, 766 (1965); (a) J. W. McFarland, C. F. Gerber, and W. M. McLamore, *ibid.*, **8**, 781 (1965); (b) J. M. McManus and C. F. Gerber, *ibid.*, **9**, 256 (1966).

(2) Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are corrected. The analyses were carried out by the Physical Measurements Laboratory of Chas. Pfizer & Co., Inc.

TABLE I

PIPERAZINESULFAMYLUREAS



No.	R_2	x	Mp, °C	Crystn solvent	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	CH_3CO	5	200–201	*a*	$C_{19}H_{29}N_4O_5S$	47.0	7.3	16.9	46.9	7.3	16.9
2	CH_3CO	6	197.5–198.5	*a*	$C_{19}H_{26}N_3O_5S$	48.5	7.6	16.2	48.7	7.6	15.9
3	CH_3CO	7	183–184	*a*	$C_{25}H_{28}N_3O_5S$	50.0	7.8	15.5	50.0	7.8	15.3
4	$(CH_3)_2CHO$	5	162.5–163.5	*a*	$C_{15}H_{25}N_3O_5S$	50.0	7.8	15.5	49.5	7.4	15.7
5	$(CH_3)_2CHCO$	6	168–169	*a*	$C_{16}H_{30}N_3O_5S$	51.3	8.1	15.0	51.2	8.0	14.8
6	$-(CH_2)_5CHCO$	6	174–175	*b*	$C_{18}H_{34}N_4O_5S$	55.0	8.3	13.5	55.0	8.4	13.2
7	CH_3OC_2HCO	5	189–190	*a*	$C_{14}H_{25}N_3O_6S$	46.4	7.2	15.5	46.3	7.2	15.7
8	CH_3OCH_2CO	6	188–189	*a*	$C_{15}H_{25}N_3O_6S$	47.6	7.5	14.9	47.9	7.8	14.9
9	$(CH_3)_2CHSCH_2CO$	5	184.5–185.5	*a*	$C_{16}H_{30}N_3O_4S_2$	47.3	7.4	13.8	46.9	7.2	13.8
10	$(CH_3)_2CHSCH_2CO$	6	188.5–189.5	*a*	$C_{17}H_{32}N_3O_4S_2$	48.5	7.7	13.3	48.7	7.6	13.0
11	CH_3CH_2NHCO	5	194–195.5	*b*	$C_{15}H_{27}N_5O_4S$	46.5	7.5	19.4	46.4	7.5	19.0
12	CH_3CH_2NHCO	6	182–183	*b*	$C_{16}H_{29}N_5O_4S$	48.0	7.8	18.7	48.3	7.2	18.5
13	CH_3SO_2	5	202–203	*a*	$C_{12}H_{23}N_4O_6S_2$	39.1	6.6	15.2	38.6	6.7	15.5
14	CH_3SO_2	6	194–195	*a*	$C_{13}H_{25}N_4O_6S_2$	40.8	6.9	14.7	40.6	7.0	15.0

[a] Not recrystallized. [b] Acetonitrile.

1-Cyclohexylcarbonyl-4-sulfamylpiperazine.—By a similar procedure 16.5 g (0.1 mole) of 1-sulfamylpiperazine and 16.1 g (0.11 mole) of cyclohexanecarbonyl chloride in 150 ml of methylene chloride containing 11.0 g (0.11 mole) of triethylamine gave 8.2 g of the desired product, mp 205–206.5°.

Anal. Calcd for $C_{11}H_{21}N_3O_3S$: C, 48.0; H, 7.7; N, 15.3. Found: C, 47.7; H, 7.5; N, 15.0.

1-Isopropylthioacetyl-4-sulfamylpiperazine.—Under a nitrogen atmosphere, 4.8 g (0.02 mole) of 1-chloroacetyl-4-sulfamylpiperazine was added to 2.3 g (0.03 mole) of 2-propanethiol and 2.2 g (0.04 mole) of sodium methoxide in 75 ml of methanol. The reaction mixture was allowed to stir for 2 hr, concentrated to one-fifth the original volume, and added to 75 ml of water. The resulting precipitate was filtered, dried, and recrystallized from ether; yield 2.3 g, mp 113–114°.

Anal. Calcd for $C_9H_{19}N_3O_3S_2$: C, 38.4; H, 6.8; N, 14.9. Found: C, 37.8; H, 6.8; N, 14.8.

1-Ethylcarbamoyl-4-sulfamylpiperazine.—To 9.9 g (0.06 mole) of 1-sulfamylpiperazine in 90 ml of DMF was added slowly 4.7 g (0.066 mole) of ethyl isocyanate and 6.6 g (0.066 mole) of triethylamine. After heating the reaction mixture for 1 hr on a steam bath it was cooled, and filtered. The desired product was recrystallized from ethanol, 7.0 g, mp 178–180°.

Anal. Calcd for $C_7H_{16}N_4O_3S$: C, 35.6; H, 6.8; N, 23.7. Found: C, 35.6; H, 6.7; N, 23.9.

1-Methylsulfonyl-4-sulfamylpiperazine.—To a solution of 1.7 g (0.01 mole) of 1-sulfamylpiperazine and 1.1 g (0.011 mole) of triethylamine in 15 ml of DMF was added 1.3 g (0.011 mole) of methanesulfonyl chloride. The reaction mixture was heated at steam bath temperatures for 1 hr followed by cooling and the addition of ether. The resulting precipitate was filtered and recrystallized from acetone, 1.0 g, mp 248–250°.

Anal. Calcd for $C_5H_{13}N_3O_4S_2$: C, 24.7; H, 5.4; N, 17.3. Found: C, 24.8; H, 5.2; N, 17.5.

Some Derivatives of Cyclododecane[1]

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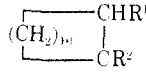
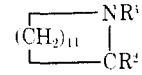
Many neuro- and psychopharmacologically active compounds contain planar, near-planar, or nonplanar cyclic moieties with acidic or basic functions in the rings or in side chains. In order to further delineate these requirements we have prepared a number of derivatives of cyclododecane with functional groups as they are encountered in typical drug molecules.

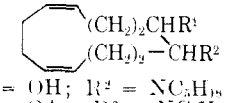
None of these compounds showed an interesting degree of biological activity in dose range studies in rats and mice.[2] Only at dose levels of 200 mg/kg in rats and 500–2000 mg/kg in mice did some of the derivatives produce overt effects such as decreased motor activity and hypotonia. None of the compounds was active in rat tests for antipyretic activity by the procedure



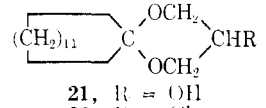
	R^1	R^2
1	$CH_2NC_5H_{10}$	=O
2	$CH_2N(CH_3)_2$	=O
3	NC_5H_{10}	H, OH
4	NC_5H_{10}	H, OAc
5	$N(CH_3)_2$	H_2
6	$NH(CH_2)_3N(C_2H_5)_2$	H_2
7	$NHCH_2C_6H_5$	H_2
8	$N^+(CH_3)_2(CH_2)_3N^-CH_3(C_2H_5)_2$	H_2
9	$N^+(CH_3)_2CH_2C_6H_4$	H_2
11	$O(CH_2)_2N(C_2H_5)_2$	H_2
12	H	OH, $(CH_2)_3N(CH_3)_2$
13	H	OH, C≡CH
14	H	OH, C≡CCH$_2$N(CH$_3$)$_2$
15	H	$OCONH_2$



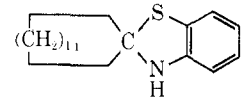
10, $R^1 = CH_3$; R^2 = H, $N^+(CH_3)_3$
16, $R^1 = (CH_2)_3N(CH_3)_2$; $R^2 = O$
17, $R^1 = (CH_2)_3N(CH_3)_2$; $R^2 = H_2$



18, R^1 = OH; $R^2 = NC_5H_{10}$
19, R^1 = OAc; $R^2 = NC_5H_{10}$
20, R^1 = OH; $R_2 = (CH_2)_3N(CH_3)_2$



21, R = OH
22, R = Cl
23, R = NC_5H_{10}



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(1) Supported by a research grant from Smith Kline and French Laboratories to whom we express our appreciation.

(2) We wish to thank Drs. D. H. Tedeschi and L. Cook of Smith Kline and French Laboratories for the performance of these tests and for permission to quote their results.