hr. After filtration, this solid was dissolved in 1.5 l. of DMF and diluted with 7 l. of 1:6 AcOH–H_2O. After filtration, digestion with 2 l. of ethanol, and filtration, the solid was dried at 110°, yield 111 g (16%) of the ester.

Dipropyl 5,5'-Dodecanedioyldiiminobis(2,4,6-triiodo-N-methylisophthalamate).—A solution of 298.5 g (0.225 mole) of **4** (R_1 = H; R_2 = CH_3; Z = $(CH_2)_{10}$) and 17.9 g of NaOH in EtOH–H_2O (1.2:0.6 l.) containing 100 ml of *n*-propyl bromide and 25 g of NaI was refluxed with stirring for 7.5 hr. The ester was isolated as described in the preceding experiment; yield 74 g (23%).

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L-, D-, and DL-Ephedrine Phosphates

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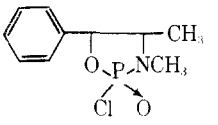
As a part of our program of synthesis of therapeutically or physiologically active compounds,[1,2] we have prepared L- (IVa), D- (IVb), and DL-ephedrine phosphates (IVc) starting from L- (Ia), D- (Ib), and DL-ephedrines (Ic).

The reaction of L-ephedrine (Ia) with phosphorus oxychloride gave L-2-chloro-3,4-dimethyl-5-phenyl-1,3,-2-oxazophospholidine 2-oxide[3] (IIa). Hydrolysis of



IIa

IIa yielded L-ephedrine phosphate (IVa) hydrochloride (IIIa) the structure of which was confirmed by catalytic hydrogenation[4] to D-N,α-dimethylphenethylamine. L-Ephedrine was obtained from the corresponding phosphate by hydrolysis; this indicates that in the course of the reactions Ia → IVa the original configuration was retained. Physical and chemical data of the compounds synthesized are reported in Table I.

Experimental Section[5]

L-2-Chloro-3,4-dimethyl-1,3,2-oxazaphospholidine 2-Oxide (IIa).—Under protection from moisture, freshly distilled L-ephedrine (16.5 g, 0.1 mole) was dissolved in triethylamine (30 ml, 0.21 mole) and in 500 ml of anhydrous benzene. With vigorous stirring, $POCl_3$ (10 ml) previously dissolved in 50 ml of anhydrous benzene was added dropwise at such a speed that the temperature of the reaction mixture remained below 50°. After stirring for 4–5 hr, the reaction mixture was filtered and the solvent was removed under reduced pressure. The dry residue was repeatedly extracted with boiling petroleum ether (bp 60–80°) and the combined extracts (about 600 ml) were cooled in the freezer for 24 hr. The precipitated white crystalline product (16.5 g) melted at 90–91° and was stable only in a dry, inert atmosphere.

L-α-[1-(Methylamino)ethyl]benzyl Phosphate Hydrochloride (L-Ephedrine Phosphate Hydrochloride, IIIa).—IIa (20 g) was suspended in 100 ml of 1 *N* HCl and heated on a water bath for 1 hr. The reaction mixture became clear after this time and was decolorized with 1 g of charcoal. The solution was evaporated under reduced pressure at 40–45° (bath temperature). The residue was suspended in acetone, filtered, and recrystallized from ethanol–ether. The white crystals (17.3 g) melted at 178–179°.

L-α-[1-(Methylamino)ethyl]benzyl Phosphate (L-Ephedrine Phosphate, IVa). A. To a solution of IIIa (56 g) in 200 ml of distilled water, Amberlite IRA-410 (OH^- form) was added until the supernatant was pH 4. The suspension was decanted and the resin was repeatedly washed with distilled water. The supernatant and the washings were evaporated under reduced pressure to dryness and from the residue, after washing with absolute ethanol and ether, 41.2 g of white crystals were obtained, mp 242–243°.

B.—Diethylamine (15 g) dissolved in 10 ml of ethanol was added to a solution of IIIa (55 g) in 300 ml of ethanol. After 12 hr at room temperature the precipitated crystals were filtered, washed with ethanol and ether, and dried; yield 42 g, mp 242–243°.

D-N,α-Dimethylphenethylamine by Catalytic Hydrogenation of IIIa.—IIIa (2.8 g) in 40 ml of ethanol was hydrogenated at atmospheric pressure and room temperature (22°) in the presence of 0.28 g of 5% Pd–C. After the uptake of the theoretical amount of hydrogen (*ca.* 2 hr), the hydrogenation was interrupted and the mixture was filtered. The solution was evaporated under reduced pressure and the residue was dissolved in 50 ml of water. The cold aqueous solution made alkaline with 30% NaOH solution was extracted with three 50-ml portions of ether. The residue, after evaporation of the solvent, distilled at 91–93° (15 mm); yield 1.2 g (84%).

The hydrochloride had mp 168–170° (lit.[6] 172°) and $[\alpha]^{20}D$ +17.2° (*c* 3.3, H_2O) [lit.[6] +17.2° (*c* 2.3, H_2O)].

The picrate had mp 142–144° (lit.[7] 145°).

Stability of L-Ephedrine Phosphate (IVa) in Aqueous Solution. IVa was dissolved in water, and the pH was adjusted in four different solutions to 2, 4, 5, and 6.5, respectively, the final concentration of IVa being always 2% w/v. The four solutions thus obtained, either by addition of NaOH or HCl, were heated separately at 100° for 10 hr. Controls by paper electrophoresis every hour showed that L-ephedrine appeared only in traces after 4 hr.

Hydrolysis of L-Ephedrine Phosphate Hydrochloride (IIIa). A solution of IIIa (5 g) in water (50 ml) was heated in a sealed tube at 120° for 3 hr. After cooling and neutralization, the water was evaporated at reduced pressure and the residue repeatedly was extracted with ether. The solvent was evaporated from the organic extracts and the residue was distilled. The fraction boiling at 132° (12 mm) was L-ephedrine (2.3 g), which was dissolved in absolute ethanol (30 ml) and mixed with normal ethanolic HCl (15 ml). The solution gave a precipitate (2.5 g) of L-ephedrine hydrochloride upon addition of 45 ml of ether; mp 215–216°; $[\alpha]D$ −36.1° (*c* 2, water).

Enzymatic Hydrolysis of L-Ephedrine Phosphate (IVa). IVa (133 mg) was dissolved in water (5 ml) and acetate buffer pH 4.5 (2 ml) containing in suspension five powdered Taka-Diastase® (Parke-Davis) tablets. After 15 hr at 40° the suspension was centrifuged, and the supernatant was analyzed by thin layer chromatography. An identical treatment was carried out on a similar reaction mixture, but without IVa. The only different spot in the first reaction mixture was L-ephedrine.

Paper Electrophoresis.—The paper used was Munktell 20 (Paperworks, Gryksbo, Sweden), the buffer employed was acetate pH 5.1, the ionic strength was 0.007, and the time was 2 hr at 200 mv. L-Ephedrine phosphate migrated slowly toward the anode; L-ephedrine migrates faster toward the cathode.

Thin Layer Chromatography.—The adsorbent used was silica gel (Merck, Darmstadt), 250 μ; the solvents were A,

(1) A. Segre and A. Larizza, *Gazz. Chim. Ital.*, **87**, 519 (1957).

(2) E. Cutillo and A. Larizza, *ibid.*, **91**, 964 (1961).

(3) For a similar reaction see: T. Bersin, H. G. Moldtmann, H. Nafiger, B. Mareband, and W. Leopold, *Z. Physiol. Chem.*, **269**, 241 (1941); Kh. Fel'dman and A. I. Berlin, *Zh. Obshch. Khim.*, **32**, 3379 (1962); *Chem. Abstr.*, **58**, 12563*g* (1963).

(4) Ia hydrochloride was unaffected under the same reaction conditions.

(5) Infrared absorption spectra were obtained on a Perkin-Elmer Infracord Model 137 spectrophotometer and ultraviolet absorption spectra on a Beckman DK-2 spectrophotometer. Melting points were determined on a Kofler block. Optical rotations were measured on a Zeiss 0.01° Kreispolaris meter. We are indebted to Miss A. De Leonibus, for microanalysis, and to Miss M. L. Reviglio for absorption spectra, chromatograms, and enzymatic hydrolysis.

(6) E. Emde, *Hoiv. Chim. Acta*, **12**, 373 (1929).

(7) H. Ogata, *J. Pharm. Soc. Japan*, 151 (1919); *Chem. Abstr.*, **14**, 745 (1920).

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	$C_{10}H_{13}ClNO_2P$	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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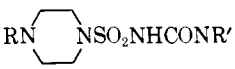
Previous publications from these laboratories[1] have demonstrated the hypoglycemic activity associated with a series of sulfamylurea and sulfamylsemicarbazides. This communication deals with the synthesis of a series of sulfamylureas in which the sulfamyl portion of the structure is derived from an 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 $C_6H_{12}ClN_3O_3S$: 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.