melted at 235.5–237°; ν_{max}^{Nujol} 1686 (s), 1633 (s) cm^{-1}. *Anal.* ($C_7H_{18}N_4S \cdot H_2SO_4$) C, H, N.

2-(2-Ethylthioethylamino)ethylguanidine Sulfate.—A solution of 7.0 g (0.082 mole) of 1-(2-aminoethyl)aziridine and 12.5 g (0.041 mole) of 2-ethyl-2-thiopseudourea sulfate in 20 ml of H_2O was left at room temperature overnight. The solvent was removed and the residue was crystallized from EtOH. The yield of white, crystalline solid was 10.2 g (52.3%): mp 151–152°; ν_{max}^{Nujol} 1670 (s), 1625 (s) cm^{-1}. *Anal.* ($C_7H_{18}N_4S \cdot 0.5H_2SO_4$) C, H, N.

2-(3-Methylthiopropylamino)ethylguanidine Sulfate.—A solution of 14.8 g (0.1 mole) of 2-(3-methylthiopropylamino)ethylamine and 13.9 g (0.05 mole) of 2-methyl-2-thiopseudourea sulfate in 25 ml of H_2O was left at room temperature overnight. The solvent was removed and the residue was crystallized from EtOH. The yield of white solid was 11.5 g (48.1%); mp 169–170°; recrystallization from EtOH raised the melting point to 173.5–174°; ν_{max}^{Nujol} 1683 (s), 1627 (s) cm^{-1}. *Anal.* ($C_7H_{18}N_4S \cdot 0.5H_2SO_4$) C, H, N.

3-(3-Methylthiopropylamino)propylguanidine Sulfate.—A solution of 22 g (0.135 mole) of 3-(3-methylthiopropylamino)propylamine and 19 g (0.068 mole) of 2-methyl-2-thiopseudourea sulfate in 35 ml of water was left at room temperature overnight. The solution was taken to dryness after 3.8 ml (0.07 mole) of concentrated H_2SO_4 had been added. The residue was crystallized twice from EtOH–H_2O to give 33.2 g (81.5%) of glistening white leaflets: mp 249–250°; ν_{max}^{Nujol} 1686 (s), 1635 (s) cm^{-1}. *Anal.* ($C_8H_{20}N_4S \cdot H_2SO_4$) C, H, N.

2-[N-Ethyl-N-(2-methylthioethyl)amino]ethylguanidine Sulfate.—A solution of 8.1 g (0.05 mole) of N-ethyl-N-(2-methylthioethyl)ethylenediamine and 7.0 g (0.025 mole) of 2-methyl-2-thiopseudourea sulfate in 10 ml of H_2O was left at room temperature overnight. To the solution was added 25 ml of 2,2-dimethoxypropane, and it was taken to dryness. The white solid which remained was collected and washed (Me_2CO). The yield was 7.0 g (57.5%): mp 70–71°; $\nu_{max}^{CHCl_3}$ 1660 (s), 1615 (sh) cm^{-1}. *Anal.* ($C_8H_{20}N_4S \cdot 0.5H_2SO_4$) C, H, N.

2-(2-Methoxyethylamino)ethylguanidine Sulfate.—A solution of 6.3 g (0.053 mole) of 2-(2-methoxyethylamino)ethylamine and 7.5 g (0.027 mole) of 2-methyl-2-thiopseudourea sulfate in 25 ml of H_2O was left at room temperature overnight. The solution was diluted with 100 ml of MeOH and 100 ml of acetone after 1.4 ml (0.025 mole) of concentrated H_2SO_4 had been added. Chilling caused 11.8 g (86%) of white, crystalline solid to precipitate: mp 254–255°; ν_{max}^{Nujol} 1684 (s), 1636 (s) cm^{-1}. *Anal.* ($C_6H_{16}N_4O \cdot H_2SO_4$) C, H, N.

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The Synthesis of Substituted Phenethylamines

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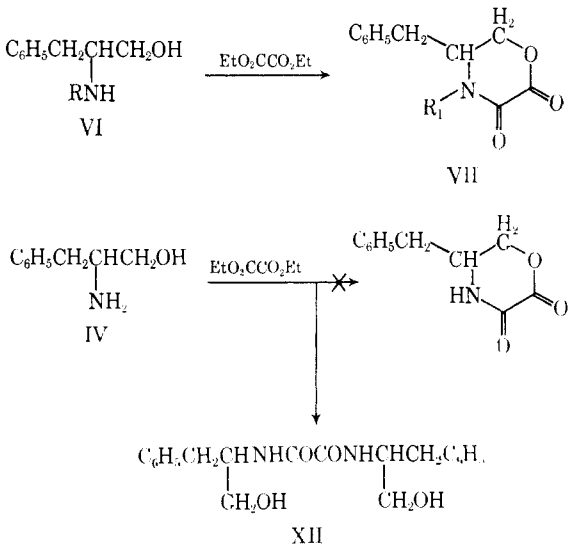
The methods of preparation and pharmacological data of a series of substituted β-phenethylamines are described.

2-Amino-3-phenyl-1-propanol (IV) was shown to possess significant analgetic activity in these laboratories. A number of compounds chemically related to this structure were prepared by the synthetic routes shown in Chart I and screened as to their analgetic, central nervous system, cardiovascular, and antiinflammatory effects.

Chemistry.—The reaction routes employed to obtain the compounds which were synthesized are found in Chart I. These compounds were derived from the *dl* form of compound I. Methods for the preparation of 2-amino-3-phenyl-1-propanol (IV),[1] ethyl 2-benzamido-3-phenylpropionate (Vb),[2] and 2-benzamido-3-phenyl-1-propanol (Xb)[3] have previously been described. 2-(*p*-Chlorobenzylamino)-3-phenyl-1-propanol (VIa) and the known 2-(benzylamino)-3-phenyl-1-propanol (VIb)[4] were synthesized by a $LiAlH_4$ reduction of Va and the known ester Vb.[4] The cyclic compounds, 5-benzyl-4-(*p*-chlorobenzyl)morpholine-2,3-dione (VIIa) and 4,5-dibenzylmorpholine-2,3-dione (VIIb), were prepared by the reaction of diethyl oxalate with VIa and VIb, respectively. The reaction of IV and diethyl oxalate yielded N,N′-bis(α-hydroxymethylphenethyl)oxamide (XII), while none of the expected product, 5-benzylmorpholine-2,3-dione, could be isolated. Apparently, under the conditions employed and based on the products isolated, the more hindered



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(2) I. Murakoshi, *J. Pharm. Soc. Japan*, **76**, 1139 (1956).
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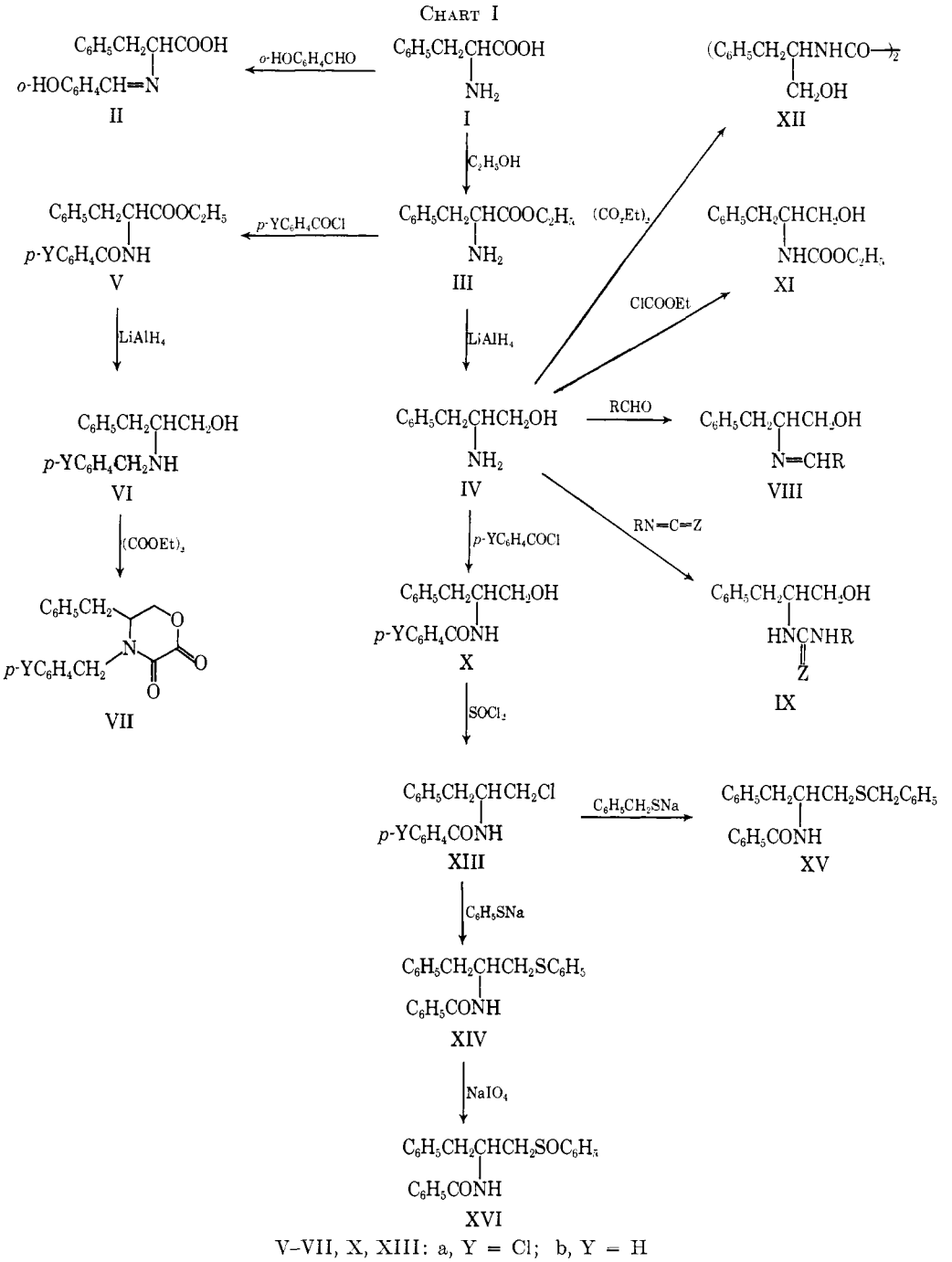
CHART I

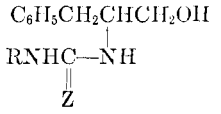


V–VII, X, XIII: a, Y = Cl; b, Y = H

benzylic secondary amines (VIa and b) preferentially undergo the intramolecular ring closure rather than the intermolecular reaction demonstrated by the primary amine (IV).

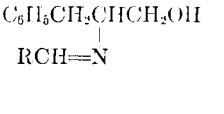
Numerous products, IXa–e, were prepared by the reaction of isocyanates and isothiocyanates with 2-amino-3-phenyl-1-propanol (IV). In all cases, the expected ureas and thioureas were formed in preference to the carbamates and thiocarbamates. Where ethyl chloroformate was used, the expected carbamate, α-(hydroxymethyl)phenethylcarbamic acid ethyl ester (XI), was isolated.

The reaction of thionyl chloride with 2-benzamido-3-phenyl-1-propanol (Xb) and 2-(*p*-chlorobenzamido)-3-phenyl-1-propanol (Xa) converted the hydroxy groups to chloro groups, resulting in the compounds, 2-benzamido-1-chloro-3-phenylpropane (XIIIb), the optically active (*R*) form of which has been reported,[5] and 2-(*p*-chlorobenzamido)-1-chloro-3-phenylpropane (XIIIa). The *dl* form had a melting point which differed from the



IX

	R	Z
a	*n*-C_4H_9	O
b	C_6H_5	O
c	C_6H_{11}	O
d	*n*-C_4H_9	S
e	C_6H_5	S



VIII

	R
a	*p*-$CH_3OC_6H_4$
b	*p*-$C_6H_5CH_2OC_6H_4$
c	*p*-FC_6H_4
d	*o*-HOC_6H_4
e	*p*-$CH_3CONHC_6H_4$
f	*p*-$CH_3C_6H_4$
g	3,4,5-$(CH_3O)_3C_6H_2$

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TABLE I

No.	Compd	General procedure	Mp, °C	Cryst solvent	% yield	Formula[a]
1	II	A	160–162 dec	THF–Et_2O	20	$C_{16}H_{15}NO_3$[b]
2	Va	B	103–104.5	EtOH	84	$C_{18}H_{18}ClNO_3$
3	VIa	C	101–103	EtOH	65	$C_{16}H_{18}ClNO$
4	VIIa	E	131–134	EtOH	22	$C_{18}H_{16}ClNO_3$
5	VIIb	E	130–132.5	C_6H_6–Et_2O	47	$C_{18}H_{17}NO_3$
6	VIIIa	A	75–77	EtOH–petr ether	26	$C_{17}H_{19}NO_2$
7	VIIIb	A	83–85	Cyclohexane	56	$C_{25}H_{23}NO_2$
8	VIIIc	A	64–66	Cyclohexane	85	$C_{16}H_{16}FNO$
9	VIIId	A	45–46.5	EtOH–petr ether	10	$C_{16}H_{17}NO_2$
10	VIIIe	A	195–197	EtOH	81	$C_{15}H_{20}N_2O_2$
11	VIIIf	A	91–93	Cyclohexane	59	$C_{17}H_{19}NO$
12	VIIIg	A	114–116	EtOH–Et_2O	50	$C_{19}H_{23}NO_4$
13	IXa	F	84–86	C_6H_6	92	$C_{14}H_{22}N_2O_2$
14	IXb	F	143–145	EtOH	96	$C_{16}H_{18}N_2O_2$
15	IXc	F	162–163	EtOH	84	$C_{16}H_{24}N_2O_2$
16	IXd	F	107–108	C_6H_6–hexane	82	$C_{14}H_{22}N_2OS$
17	IXe	F	171–173	C_6H_6	83	$C_{16}H_{18}N_2OS$
18	Xa	B	144–146	EtOH–C_6H_6	64	$C_{16}H_{16}ClNO_2$
19	XI	B	74–76	EtOH	16	$C_{23}H_{21}NO_3$
20	XII	E	225–227	THF	38	$C_{26}H_{30}N_2O_4$
21	XIIIa	D	126–128	EtOH	71	$C_{16}H_{15}Cl_2NO$
22	XIIIb	D	106–108	EtOH	38	$C_{16}H_{16}ClNO$
23	XIV	G	144–146		39	$C_{32}H_{31}NOS$
24	XV	G	144–145.5		44	$C_{23}H_{23}NOS$
25	XVI	H	169–171		58	$C_{29}H_{29}NO_2S$

[a] All compounds were analyzed for C, H, N. [b] C: calcd, 71.36; found, 71.81.

reported compound[6] by 26°. Compound XIIIb was used as a starting material to prepare a number of sulfur derivatives (XIV–XVI).

Since a low order of analgetic activity of the Schiff base, 3-phenyl-2-(*p*-methoxybenzylideneimino)-1-propanol (VIIIa), was observed, a number of compounds of this type were prepared (VIIIb–g) in hopes of increasing the activity.

Pharmacology.—The compounds reported in this paper were administered orally and screened for antihypertensive activity in renal hypertensive rats,[6] antiinflammatory activity in the carrageenin abscess test[7] in rats, and analgetic activity in the phenylquinone-induced writhing test in mice.[8] General symptomatology and toxicity were observed in dose range studies in mice.

2-Amino-3-phenyl-1-propanol (IV) demonstrated activity (ED_{50} = 46 mg/kg) in the phenylquinone writhing test. 3-Phenyl-2-(*p*-methoxybenzylideneimine)-1-propanol (VIIIa) also showed activity in this test (ED_{50} = 70 mg/kg); subsequent screening in the hot plate test[9] showed a low order of activity (500 mg/kg) and a lack of activity in the Randall–Selitto test[10] using the noninflamed paw. In mice, the minimal lethal dose was greater than 1 g/kg and the minimal symptomatic dose was 125 mg/kg.

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(8) L. C. Hendershot and J. Forsaith, *J. Pharmacol. Exptl. Therap.*, **125**, 237 (1959).

(9) N. B. Eddy and D. Leimbach, *ibid.*, **107**, 385 (1953).

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Experimental Section

Where analyses are indicated, analytical results obtained for those elements were within ±0.4% of the theoretical values. Absorption bands in the infrared spectra were as expected. See Table I for physical and analytical data.

A. General Preparation of II and VIIIa–g.—A solution of amine (0.05 mole), aldehyde (0.05 mole), *p*-toluenesulfonic acid (catalytic quantity), and C_6H_6 (300 ml) was heated under reflux until 0.9 ml of H_2O was collected in a Dean–Stark trap. After permitting the reaction to come to room temperature, it was extracted twice with a saturated $NaHCO_3$ solution (200 ml), dried, filtered, and concentrated under reduced pressure. The resulting oils were solidified by trituration with petroleum ether (bp 30–60°) or ether.

B. General Preparation of Va, Xa, and XI.—To a stirred and cooled solution of the amine (0.1 mole) and Et_3N (0.3 mole) in C_6H_6 (600 ml), the acid chloride (0.1 mole) dissolved in C_6H_6 (100 ml) was added dropwise. After stirring at room temperature overnight, H_2O (400 ml) was added. Compound Xa separated and was filtered directly while Va and XI remained in the C_6H_6 layer which was separated and combined with the C_6H_6 extracts of the aqueous portion, dried, filtered, and concentrated under reduced pressure. The resulting oils were solidified by trituration with cyclohexane.

C. General Preparation of VIa and VIb.—The amide (0.1 mole) was dissolved in dry THF (300 ml) and added, dropwise, over a 1-hr period to a stirred suspension of $LiAlH_4$ (0.2 mole) in dry THF (700 ml) which was immersed in an ice bath. The reaction mixture was then refluxed for 4 hr. After cooling in an ice bath, the complex was decomposed by the dropwise addition of a 10% aqueous NaOH solution (50 ml) followed by a saturated aqueous solution of Na_2SO_4 (50 ml). After stirring for 45 min, anhydrous Na_2SO_4 (15 g) was added. The reaction mixture was filtered and dried with additional Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was crystallized by treatment with heptane. Compound VIb was recrystallized from EtOH in an 88% yield, mp 68–69° (lit.[4] 69–71°).

D. General Preparation of XIIIa and XIIIb.—A mixture of alcohol (0.05 mole), $SOCl_2$ (0.1 mole), pyridine (catalytic quantity), and C_6H_6 (500 ml) was heated under reflux for 4 hr. The reaction mixture was concentrated under reduced pressure. The resulting oil was solidified by trituration with petroleum ether or ether.

E. General Preparation of VIIa, VIIb, and XII.—The amino alcohol (0.05 mole) and ethyl oxalate (0.05 mole) were heated together in PhMe (500 ml) and the solvent (300 ml) was distilled off over a 10-hr period removing the EtOH as it was formed. After removal of the remaining solvent, under reduced pressure, the oily residue was solidified by trituration with cyclohexane.

F. General Preparation of IXa–e.—To a solution of the amine (0.05 mole) in C_6H_6 (100 ml), a solution of isocyanate or isothiocyanate (0.05 mole) in C_6H_6 (50 ml) was added and the reaction was permitted to stand for 16 hr. Where crystallization could not be directly induced in the reaction mixture, the solvent was removed and the residue was treated with petroleum ether to give a solid material.

G. General Preparation of XIV and XV.—To a solution of EtONa (0.05 mole) in EtOH (100 ml), the thiol (0.05 mole) dissolved in EtOH (50 ml) was added. After 15 min, the chloro compound (0.05 mole) dissolved in EtOH (200 ml) was added, followed by 5 hr of refluxing. The NaCl formed was filtered from the hot solution and on cooling, crystals of the pure product were deposited.

H. Phenyl (2-Benzamido-3-phenyl)-1-propyl Sulfoxide (XVI).—To a cold solution of $NaIO_4$ (0.011 mole) in H_2O (50 ml), a solution of XVI (0.01 mole) in MeOH–EtOH (100 ml) was added and permitted to stand for 4 days. After filtration, the filtrate was extracted with $CHCl_3$. The $CHCl_3$ layer was dried, filtered, and concentrated under reduced pressure resulting in a solid material.

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