TABLE I
INHIBITION OF MAO BY $C_6H_5CHOHCH_2NHR_2$ (R^1)

Compd	R^1	R^2	I_{50}, mM
1·tartrate	H	H	0.16
2·HCl	$CO_2C_2H_5$	H	7.8
3·HCl	H	$CO_2C_2H_5$	5.4
4·HCl	$CO_2C_2H_5$	$CO_2C_2H_5$	16.0

Discussion.—The potency order of **1** > **3** > **2** > **4** is consistent with accepted structure–activity relationships for MAO inhibition in phenylethylhydrazine molecules.[8] The presence of a carbethoxy group on either N adversely affects the *in vitro* MAO inhibitory potency. The discrepancy between the *in vitro* activity of **1** observed in this study and the results of Biel, *et al.*,[4] may be due to the use of different substrates.

Experimental Section[9]

2-Hydroxy-2-phenylethylhydrazine (1).—The method of Benoit[2] was employed. The oxalate salt, mp 170° [*Anal.* ($C_{10}H_{14}N_2O_5$) C, H, N], and the tartrate salt, mp 141–143°, were recrystallized from MeOH–Et_2O.

N^1-Carbethoxy(2-hydroxy-2-phenyl)ethylhydrazine (2) was synthesized by treating **1** with ethyl chloroformate as described by Matzner, *et al.*[10] The HCl salt was recrystallized from $CHCl_3$–EtOAc; yield 76%, mp 134–136°. *Anal.* ($C_{11}H_{17}ClN_2O_3$) C, H, N.

N^2-Carbethoxy(2-hydroxy-2-phenyl)ethylhydrazine (3).—To a solution of styrene bromohydrin (2.42 g, 0.012 mole) in 100 ml of EtOH was added a solution of ethyl carbazate (1.4 g, 0.0133 mole) in 50 ml of EtOH. The solution was refluxed overnight, evaporated under reduced pressure, and treated with 20 ml of 10% $NaHCO_3$ solution and 200 ml of EtOH. The precipitate was removed and the solution was evaporated to yield **3** as an oil, yield 70%). The oxalate, mp 112–115° [*Anal.* ($C_{13}H_{18}N_2O_7$) C, H, N], and the HCl salt, mp 108–110°, were recrystallized from MeOH–Et_2O.

N^1,N^2-Dicarbethoxy(2-hydroxyl-2-phenyl)ethylhydrazine (4).—To a cold solution of **2** (4.0 g, 0.018 mole) in 150 ml of Et_2O was added ethyl chloroformate (2.95 g, 0.027 mole) in 100 ml of Et_2O. After stirring for 2 hr the product (**4**) was removed by filtration. The HCl salt, mp 142–143°, yield 65%, was recrystallized from $CHCl_3$–EtOAc. *Anal.* ($C_{14}H_{21}ClN_2O_5$) C, H, N.

Acknowledgments.—The excellent technical assistance of Mr. Edward Fritchie is acknowledged by W. M. I. and B. T. H. This project was supported in part by Grant MH-08737 from the National Institute of Mental Health and Grant GY-2552 from the National Science Foundation.

(8) B. M. Bloom, *Ann. N. Y. Acad. Sci.*, **107**, 878 (1963).

(9) Melting points were determined on a Hoover apparatus and are uncorrected. Where analyses are indicated by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(10) M. Matzner, R. P. Kurkjy, and R. S. Cotter, *Chem. Rev.*, **64**, 645 (1964).

Thiomethyltetrazole Hypoglycemic Agents

J. M. McMANUS

Medical Research Laboratories, Chas. Pfizer & Co., Inc., Groton, Connecticut

Received November 27, 1968

A report[1] of the potentiation of insulin hypoglycemia by a series of phenylsulfinyl- and -sulfonylacetic acid derivatives prompted us to synthesize and test for hypoglycemic effects a group of related congeners in which the carboxyl group was replaced by an acidic, 5-tetrazolyl moiety.[2] It was anticipated that the tetrazole would impart the same degree of acidity[3] to the resulting compounds as the carboxyl group but would not undergo the facile decarboxylation typical for β-sulfinyl- and β-sulfonylacetic acids (Table I).

A series of alkyl-, aralkyl- and arylthioacetonitriles (Table II), prepared by alkylation of the requisite mercaptan with chloroacetonitrile, was converted to the corresponding tetrazoles using the method of Finnegan, *et al.*[4] Oxidation of the resulting thiomethyltetrazoles using H_2O_2 in AcOH provided a route to the desired sulfones.

Titration in 1:1 dioxane–water showed the thiomethyltetrazoles to be weak acids; the sulfonylmethyl congeners, because of the inductive effect of the sulfone group, were somewhat more acidic, differing from the sulfides by more than 1 pK_a unit. Compound **2** gave an anomalous titration curve which was indicative of a dibasic acid with a neutralization equivalent approximately one-half the calculated value. It is probable that the CH_2 group, flanked by the CF_3 and SO_2 moieties, is sufficiently acidic to be titrated along with the tetrazole. The absence of a discernible double break in the titration curve prevented meaningful calculation of pK_{a_1} and pK_{a_2}.

None of the compounds showed any hypoglycemic activity when screened according to previously described procedures.[5]

Experimental Section[6]

5-(2,2,2-Trifluoroethylthiomethyl)tetrazole.—A mixture of 3.1 g (0.02 mole) of 2,2,2-trifluoroethylthioacetonitrile,[7] 2.16 g (0.04 mole) of NH_4Cl, 2.8 g (0.044 mole) of NaN_3, and 0.02 g of LiCl in 15 ml of DMF was heated at steam-bath temperatures overnight. The reaction mixture was cooled, diluted with 30 ml of H_2O, and acidified with concentrated HCl to pH 3–4. The precipitated solid was filtered and dried, 2.5 g.

The thiomethyltetrazoles were prepared by a similar procedure in yields of 60–90%; they are listed with their physical properties in Table I.

5-(Isopropylsulfonylmethyl)tetrazole.—To a solution of 11.8 g (0.075 mole) of 5-(isopropylthiomethyl)tetrazole in 75 ml of glacial AcOH was added 19 g of 30% H_2O_2 dropwise over a period of 15 min. The reaction mixture was stirred at room temperature overnight, and was then heated at steam-bath temperature for 15 min. The solution was cooled, and the product precipitated by the addition of pentane.

The sulfones listed in Table I were all prepared by a similar procedure in 40–60%.

***p*-Chlorophenylthioacetonitrile.**—To a suspension of 59 g (0.42 mole) of *p*-chlorothiophenol and 55 g (0.42 mole) of K_2CO_3 in 275 ml of 1,2-dimethoxyethane was added, dropwise, 32 g (0.42 mole) of chloroacetonitrile. The resulting mixture was stirred for 1 hr, and was then refluxed overnight. Most of the solvent was removed under reduced pressure followed by the addition of

(1) E. Riesz, W. Wolf, and H. Alvarez, *Bull. Soc. Chim. France*, 1057 (1963).

(2) R. M. Herbst in "Essays in Biochemistry", S. Graff, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, pp 141–155.

(3) J. S. Mihina and R. M. Herbst, *J. Org. Chem.*, **15**, 1082 (1950).

(4) W. G. Finnegan, R. A. Henry, and R. Lofquist, *J. Am. Chem. Soc.*, **80**, 3908 (1958).

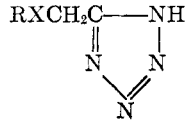
(5) J. M. McManus, J. W. McFarland, C. F. Gerber, W. M. McLamore, and G. D. Laubach, *J. Med. Chem.*, **8**, 766 (1965).

(6) 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. Titrations were done in 1:1 (v/v) dioxane–water using a Metrohm potentiograph Model E436. Where analyses are indicated only by symbols of elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(7) J. M. McManus, *J. Heterocycl. Chem.*, **5**, 137 (1968).

TABLE I

THIO- AND SULFONYLMETHYLTETRAZOLES



No.	R	X	Mp, °C	Crystn solvent	Formula[e]	Apparent pK_a
1	CF_3	S	99.5–100.5	*a*	$C_4H_5F_3N_4S$	4.9
2	CF_3	SO_2	195–196	*a*	$C_4H_5F_3N_4O_2S$	
3	$(CH_3)_2CH$	S	109–110	*a*	$C_5H_{10}N_4S$	5.4
4	$(CH_3)_2CH$	SO_2	155.5–156.5	*b*	$C_5H_{10}N_4O_2S$	4.0
5	3-Thienyl	S	129–130	*a*	$C_6H_6N_4S_2$	5.3
6	3-Thienyl	SO_2	160 dec	*a*	$C_6H_6N_4O_2S_2$	4.2
7	*p*-ClC_6H_4	S	159–160	*a*	$C_8H_7ClN_4S$	5.1
8	*p*-ClC_6H_4	SO_2	225 dec	*c*	$C_8H_7ClN_4O_2S$	4.0
9	*p*-$ClC_6H_4CH_2$	S	103–104	*a*	$C_9H_9ClN_4S$	5.3
10	*p*-$ClC_6H_4CH_2$	SO_2	234 dec	*d*	$C_9H_9ClN_4O_2S$	4.0
11	*p*-$CH_3C_6H_4$	S	142–143	*a*	$C_9H_{10}N_4S$	5.3
12	*p*-$CH_3C_6H_4$	SO_2	211 dec	*c*	$C_9H_{10}N_4O_2S$	4.2

[a] Et_2O. [b] EtOAc. [c] H_2O. [d] Me_2CO. [e] All compounds were analyzed for C, H, N, and neut equiv.

TABLE II

THIOACETONITRILES

$RSCH_2CN$

R	Mp or bp (mm), °C	Formula[c]
$(CH_3)_2CH$	88–90 (23)	C_5H_9NS
3-thienyl	96 (0.1)	$C_6H_5NS_2$
p-ClC_6H_4[a]	84–85	C_8H_6ClNS
p-$ClC_9H_4CH_2$	109 (0.1)	C_9H_8ClNS
p-$CH_3C_6H_4$[b]	41–42	C_9H_9NS

[a] E. A. Falco, B. Roth, and G. H. Hitchings, *J. Org. Chem.*, **26**, 1143 (1961). [b] J. M. van der Zanden, J. Nieuwenhuis, and H. J. T. Bos, *Rec. Trav. Chim.*, **76**, 669 (1957). [c] All compounds were analyzed for C, H.

300 ml of H_2O, and 300 ml of Et_2O. The ether layer was separated, dried ($MgSO_4$), and concentrated to dryness *in vacuo*. The residue was triturated with pentane and filtered.

The thioacetonitriles listed in Table II were synthesized by analogous procedures.

Potential Antihypertensive Agents. IV.[1] Unsymmetrically 1,4-Disubstituted Piperazines. II

RAJ NANDAN PRASAD AND KARIN TIETJE

Research Department, Abbott Laboratories Ltd., Montreal, Quebec, Canada

Received January 7, 1969

In these laboratories, for a number of years, we have been interested in piperazine derivatives as antihypertensive agents. This report presents the syntheses of several 1-alkyl- (or 1-aryl- or 1-aralkyl-) 4-N-substituted carbamoyl- (or thiocarbamoyl-, ureido-, or thioureido-) piperazines and the evaluation of their biological activities.

The compounds prepared and tested in this series are listed in Tables I and II. The N-substituted carbamoyl and thiocarbamoyl derivatives (**1–11**, Table I) were obtained by the reaction of the monosubstituted piperazines with the corresponding isocyanates or isothiocyanates in a suitable solvent.

(1) For paper III, see R. N. Prasad, *J. Med. Chem.*, **12**, 290 (1969).

Reaction of 1-methylhomopiperazine with benzyl isothiocyanate, however, gave an oil which could not be induced to crystallize. Treatment of the oil with MeI gave methyl N-benzyl-4-methyl-1-homopiperazinethiocarboximidate (**12**) as a hydriodide salt in 24% over-all yield. Other S-methyl derivatives (**13**, **14**) were prepared from the corresponding thiocarbamoyl derivatives (**7**, **6**) in excellent yields. Reaction of **13** with methanolic NH_3 gave N-cyclohexyl-4-phenyl-1-piperazinecarboxamidine (**15**) in poor yield.

The thioureido and ureido derivatives (**16–25**, Table II) were prepared similarly from 1-substituted 4-aminopiperazines. Reaction of some 1-substituted 4-(β-aminoethyl)piperazines with isothiocyanates similarly gave the corresponding thioureas (**26–28**, Table II).

Pharmacology.—The piperazines were evaluated for antihypertensive activity by the method reported before.[2] Of these, only **1**, **5**, **6**, and **26** showed a sustained moderate decrease in blood pressure at 5–10 mg/kg. Compounds **4**, **7**, **10–12**, **16**, and **20** caused an unsustained fall in blood pressure, whereas **19** produced a transient hypertensive effect. The remaining compounds were inactive.

Experimental Section[3]

Following are representative examples of the preparative methods employed. The solvents used in the preparation and the reaction periods are indicated in Tables I and II.

Method A. 1-(N-Cyclohexylcarbamoyl)-4-phenylpiperazine (1).—A solution of cyclohexyl isocyanate (13.7 g, 0.11 mole) in Et_2O (300 ml) was added dropwise (under anhydrous conditions) to a well-stirred solution of N-phenylpiperazine (16.2 g, 0.1 mole) in C_6H_6 (200 ml) at room temperature. The mixture was refluxed for 0.5 hr and the product was filtered. One recrystallization (C_6H_6) gave the pure product (Table I).

Method B. 1-(N-Benzylthiocarbamoyl)-4-phenylpiperazine (6).—A solution of benzyl isothiocyanate (18.4 g, 0.123 mole) in Et_2O (50 ml) was added to a solution of N-phenylpiperazine (20 g, 0.123 mole) in Et_2O (200 ml) at 10–20°. The mixture was stirred for 0.25 hr, allowed to stand 15 hr at room temperature,

(2) F. Fried, R. N. Prasad, and A. P. Gaunce, *ibid.*, **10**, 279 (1967).

(3) All melting points were determined in open capillary tubes with a Thomas–Hoover capillary melting point apparatus and are corrected. The elemental analyses were performed by Messrs. Orville Kolsto and Victor Rauschel and Staff of Abbott Microanalytical Laboratory, North Chicago, Ill. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.