Inhibitors of Phenylethanolamine N-Methyltransferase and Epinephrine Biosynthesis. 2. 1,2,3,4-Tetrahydroisoquinoline-7-sulfonanilides[1]

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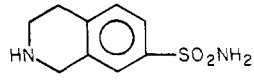
1,2,3,4-Tetrahydroisoquinoline-7-sulfonanilides (1-14) related to 1,2,3,4-tetrahydroisoquinoline-7-sulfonamide (21, SK&F 29661) were prepared and studied for their ability to inhibit phenylethanolamine N-methyltransferase (PNMT) in vitro. The choice of substituents on the 7-phenyl group of the sulfonanilides was based on the Topliss approach to structure-activity relationship studies. Information about the importance of an acidic hydrogen atom on the sulfonamide nitrogen atom was obtained from the preparation and testing of a tertiary N-methylsulfonanilide (15). Other THIQ's (1,2,3,4-tetrahydroisoquinolines) containing sulfur substituents in the 7 position were prepared and tested and consisted of 7-N-benzyl and 7-N-phenethyl derivatives of SK&F 29661 (16-18) and 7-(phenacylthio)- and 7-(phenacylsulfonyl)-THIQ (19 and 20). The two most potent inhibitors were the 7-p-bromo- and p-chlorosulfonanilides, 2 and 6. However, neither was an effective inhibitor of norepinephrine to epinephrine conversion when tested in an in vivo mouse assay at unit doses of 25 or 100 mg/kg.

The final step in the biosynthesis of epinephrine is the N-methylation of norepinephrine (NE). This conversion is catalyzed by the enzyme phenylethanolamine N-methyltransferase (PNMT, norepinephrine N-methyltransferase, EC 2.1.1.28) and involves the transfer of a methyl group from S-adenosylmethionine to NE. It has been postulated that specific inhibitors of this transfer would have therapeutic value in several clinical situations,[2] namely, the treatment of angina pectoris, myocardial infarction, anxiety, and hypertension. The initial searches for such agents uncovered several compounds with potent in vitro activity.[2-7] Subsequent work led to compounds that were also effective in vivo.[8-11]

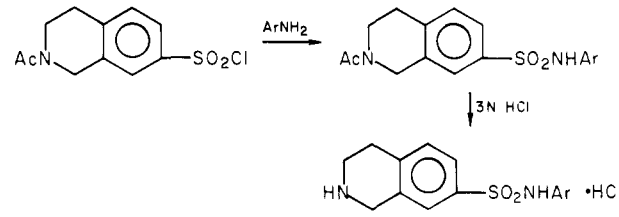
Recently, 1,2,3,4-tetrahydroisoquinoline-7-sulfonamide (21, SK&F 29661) was shown to be an effective inhibitor



21

of PNMT.[12] 21 is a potent inhibitor of PNMT after systemic administration to rats and mice, in all organ systems examined except the brain.[12] It is assumed that the overall polarity of this molecule prevents its traversal of the blood-brain barrier and thus prevents its entry into the CNS. This property of 21 provoked interest in related structures.

Scheme I



One of the most convenient and best understood ways of altering the electronic and lipophilic properties of an active chemical species is to manipulate substituents on a phenyl ring. Thus, a series of sulfonanilides related to 21 was prepared to explore the effects of this structural modification on PNMT-inhibitory activity. This plan was carried out systematically using guidelines suggested by Topliss.[13]

It had been found earlier in our laboratories that replacing the sulfonamide hydrogens of 21 with methyl groups led to compounds with decreased PNMT-inhibitory activity.[14] Further proof of this finding was sought with the preparation of a tertiary sulfonanilide. In addition, three 7-N-aralkyl derivatives of 21 and two 7-phenacyl sulfur compounds were prepared to gain some further insight into the structural requirements for PNMT-inhibitory activity.

Chemistry. The sulfonanilides were prepared straightforwardly in two steps starting with 2-acetyl-1,2,3,4-tetrahydroisoquinoline-7-sulfonyl chloride (2-Ac-THIQ-7-SO_2Cl) (Scheme I).[12,15] The intermediate 2-acetyl-1,2,3,4-tetrahydroisoquinoline-7-sulfonanilides resulting from the reaction of 2-Ac-THIQ-7-SO_2Cl with various anilines were hydrolyzed in dilute hydrochloric acid to give the desired products directly as hydrochloride salts. The 1,2,3,4-tetrahydroisoquinoline-7-sulfonanilides prepared (1-14) are listed in Table I together with appropriate analytical data and physical constants. The intermediate

(1) For part 1, see W. E. Bondinell, F. W. Chapin, G. R. Girard, K. G. Holden, C. Kaiser, A. M. Pavloff, R. G. Pendleton, M. S. Schwartz, J. S. Silvestri, and P. D. Vaidya, in "Abstracts of Papers", 178th National Meeting of the American Chemical Society, Washington, D.C., Sept., 1979, American Chemical Society, Washington, D.C., 1979, Abstr. MEDI 12; *J. Med. Chem.*, **23**, 506 (1980).
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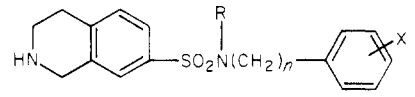
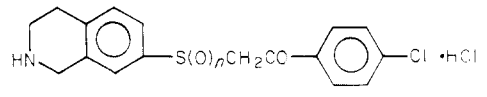
Table I. 1,2,3,4-Tetrahydroisoquinoline-7-sulfonamide Hydrochlorides



1-18



19, 20

no.	X	R	n	mp, °C	recrystn solvent	% yield	formula[a]	in vitro inhibn of PNMT,[b] % inhibn at 10^{-4} M	in vitro inhibn of PNMT,[b] % inhibn at 10^{-6} M
1	H	H	0	228-230	MeOH-Et_2O	60	$C_{15}H_{16}N_2O_2S$	76	6
2	*p*-Cl	H	0	237-239	EtOH	49	$C_{15}H_{15}ClN_2O_2S$	99	69
3	*p*-Me	H	0	185	EtOH-EtOAc	63	$C_{16}H_{18}N_2O_2S$[c]	98	22
4	*p*-OMe	H	0	242-244	MeOH-Et_2O	74	$C_{16}H_{18}N_2O_3S$	65	0
5	3,4-Cl_2	H	0	251-255	*i*-PrOH-Et_2O	58	$C_{15}H_{14}Cl_2N_2O_2S$[c]	98	30
6	*p*-Br	H	0	243-245	MeOH-Et_2O	67	$C_{15}H_{15}BrN_2O_2S$	100	78
7	*m*-CF_3	H	0	214-216	EtOH-Et_2O	59	$C_{16}H_{15}F_3N_2O_2S$	54	
8	3,4-Me_2	H	0	224-226	EtOH	89	$C_{17}H_{20}N_2O_2S$[d]	73	
9	*p*-CF_3	H	0	241-243	*i*-PrOH-Et_2O	49	$C_{16}H_{15}F_3N_2O_2S$	96	28
10	3-CF_3, 4-Cl	H	0	270-272	EtOH	64	$C_{16}H_{14}ClF_3N_2O_2S$	53	19
11	*o*-Cl	H	0	174-175	*i*-PrOH	52	$C_{15}H_{15}ClN_2O_2S$[e]	77	2
12	*m*-Cl	H	0	222-225	*i*-PrOH	54	$C_{15}H_{15}ClN_2O_2S$	72	0
13	*p*-CO_2H	H	0	259-260[f]	MeOH	15	$C_{16}H_{16}N_2O_4S$[c]	17	1
14	2,3-Cl_2	H	0	281-282	EtOH-Et_2O	70	$C_{15}H_{14}Cl_2N_2O_2S$	12	8
15	*p*-Cl	CH_3	0	219-220	MeOH	47	$C_{16}H_{17}ClN_2O_2S$	79	0
16	H	H	1	212-214	EtOH	51	$C_{16}H_{18}N_2O_2S$	66	1
17	H	H	2	205-207	EtOH	37	$C_{17}H_{20}N_2O_2S$[g]	51	6
18	*p*-Cl	H	2	226-228	EtOH	37	$C_{17}H_{19}ClN_2O_2S$	44	3
19			0	224-226	MeOH	69	$C_{17}H_{16}ClNOS$	69	1
20			2	280-281	H_2O	81	$C_{17}H_{16}ClNO_3S$	22	0
21								100	54

[a] Analyses (C, H, and N) for compounds listed in this table were within ±0.4% of the theoretical values unless otherwise noted. Melting points were determined in a Thomas-Hoover melting point apparatus or an electrically heated metal block and are uncorrected. [b] A partially purified, lyophilized PNMT preparation derived from rabbit adrenals was obtained commercially from Accurate Chemical Co., Hicksville, N.Y. The enzyme was solubilized in potassium phosphate buffer and the reaction was run in 300 μL, constituted as follows: PNMT, 280 μg; phosphate buffer (pH 7.4), 50 μmol; *l*-norepinephrine, 9 nmol; and *S*-[^{14}C]adenosylmethionine (SAM, ~20 000 dpm), 9 nmol. The label was localized on the reactive methyl group of the SAM molecule. The reaction was run for 15 min at 37 °C, following which it was terminated with 1 N HCl (200 μL). Approximately 0.5 g of solid NaCl was then added and the solution was extracted with 6 mL of acid-washed 1-butanol. One milliliter of the butanol layer, containing labeled epinephrine product, was then added to 10 mL of an aqueous phosphor (Instabray, Yorktown Research, Hackensack, N.J.), counted in a Nuclear-Chicago liquid scintillation spectrophotometer for 10 min, and quantitated in terms of nanomoles of epinephrine. The recovery of epinephrine in the butanol phase in this assay is 69 ± 0.8%; all results are appropriately corrected. The assay is linear with respect to both time and protein concentrations; the number of counts in the control samples were 419 ± 12 dpm above the blanks. The nonenzymatic destruction of norepinephrine was 9%. A correction was made for the small amount of SAM (79 ± 4 dpm) coming through the extraction procedure. Results were corrected for quenching by the use of internal standards. [c] Contains 0.25 mol of H_2O. [d] C: calcd, 57.86; found, 57.37. [e] Hemihydrate. [f] Melts with decomposition. [g] Contains 0.75 mol of H_2O.

2-acetyl derivatives are listed similarly in Table II. In one instance, the preparation of **14**, the trifluoroacetyl group was used as a protecting group to see if it offered any advantages over the acetyl group. None was apparent.

In order to obtain an example of a tertiary sulfonanilide, 7-*N*-(*p*-chlorophenyl)-7-*N*-methyl-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide (**15**) was prepared by methylation and acid hydrolysis of the 2-acetyl derivative of **2**.

The above studies were supplemented by a smaller study to determine how PNMT-inhibitory activity was affected by modifying the 7-sulfonanilide group of **1** and **2**. Thus, three 7-*N*-aralkyl sulfonamides were synthesized (**16–18**, Table I) using the procedure described for the preparation of **1–14**, with substituted aralkylamines used in place of substituted anilines.

Two 7-(phenacylthio)-THIQ's were derived from 2-Ac-THIQ-7-SH, which was obtained in turn by stannous chloride reduction of 2-Ac-THIQ-7-SO_2Cl. The crude, easily oxidized mercaptan was alkylated promptly with ω-bromo-*p*-chloroacetophenone. The resulting reaction mixture was purified by column chromatography to give 2-Ac-THIQ-7-SCH_2CO-*p*-ClPh, which was oxidized to the corresponding sulfone. Acid-catalyzed deacetylations of the thio and sulfonyl intermediates gave the THIQ's **19** and **20** (Table I).

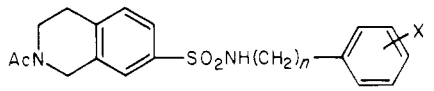
Discussion

The initial set of compounds (**1–5**) suggested in the Topliss approach to structure–activity relationship studies[13] indicated that the probably operative, potency-dependent parameter was either $2\pi - \pi^2$ or $\pi + \sigma$ (*p*-Cl = 3,4-Cl_2 > *p*-CH_3 > H = *p*-OCH_3; **2** = **5** > **3** > **1** = **4**). If $2\pi - \pi^2$ was the operative determinant, greater potency was predicted for **6–8** (*p*-Br, *m*-CF_3, 3,4-Me_2). If $\pi + \sigma$ was the important variable, then **9** and **10** with the substituents *p*-CF_3 and 3-CF_3, 4-Cl should be more potent compounds.

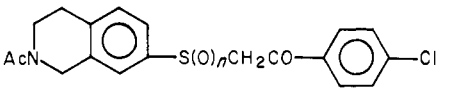
The biological data (Table I), however, do not offer a clear-cut distinction between the two choices (compare **6** with **9** and **8** with **10**). It appears that a steric factor may be involved, in that meta-substituted compounds are less potent than the corresponding para-substituted compounds (**2** vs. **12** and **9** vs. **7**), and the 3,4-disubstituted analogues are less potent than similar para-monosubstituted compounds (**2** vs. **5**, **2** or **9** vs. **10**).

Four compounds (**11–14**), not suggested by the apparent dependency parameters, were prepared and tested in the

Table II. 2-Acetyl-1,2,3,4-tetrahydroisoquinoline-7-sulfonamides



X	n	mp, °C	recrystn solvent	% yield	formula[a]
H	0	177-179	EtOH	38	$C_{17}H_{18}N_2O_3S$
p-Cl	0	199-200	i-PrOH	46	$C_{17}H_{17}ClN_2O_3S$
p-Me	0	167-169	$CHCl_3$	41	$C_{18}H_{20}N_2O_3S$
p-OMe	0	145-147	MeOH	42	$C_{18}H_{20}N_2O_4S$
3,4-Cl_2	0	184-186	MeOH-i-PrOH	43	$C_{17}H_{16}Cl_2N_2O_3S$
p-Br	0	168-170	MeCN	57	$C_{17}H_{17}BrN_2O_3S$
m-CF_3	0	162-163	i-PrOH	46	$C_{18}H_{17}F_3N_2O_3S$
3,4-Me_2	0	152-154	C_6H_5Me	42	$C_{19}H_{22}N_2O_3S$
p-CF_3	0	160-165	i-PrOH-Et_2O	48	$C_{18}H_{17}F_3N_2O_3$
3-CF_3, 4-Cl	0	170-172	EtOH	26	$C_{18}H_{16}ClF_3N_2O_3S$
o-Cl	0	140-142	i-PrOH	33	$C_{17}H_{17}ClN_2O_3S$
m-Cl	0	154-156	i-PrOH	48	$C_{17}H_{17}ClN_2O_3S$
p-CO_2Et	0	162-164	i-PrOH-Et_2O	36	$C_{20}H_{22}N_2O_5S$
p-CO_2H	0	244-249	MeOH	62	$C_{18}H_{18}N_2O_5S$[b]
2,3-Cl_2	0	141-143	c	30	$C_{17}H_{13}Cl_2F_3N_2O_3S$[d]
p-Cl	2	122-124	EtOH	38	$C_{19}H_{21}ClN_2O_3S$



	0	104-106	MeOH	25	$C_{19}H_{18}ClNO_2S$
	2	150-152	MeCN	76	$C_{19}H_{18}ClNO_4S$

[a] See footnote a, Table I. [b] Hemihydrate. [c] Washed with Et_2O and petroleum ether (bp 40-60 °C). [d] Trifluoracetyl derivative.

PNMT assay to examine possible steric interactions (**11**, **12**, and **14**) and the effect of an anionic binding site (**13**). These compounds, for the most part, were significantly less potent.

The idea that an acidic sulfonamido hydrogen atom was important in eliciting PNMT-inhibitory activity was based on findings noted with **21** and its sulfonamide *N*-methyl and *N,N*-dimethyl derivatives. The derivatives caused, respectively, an 87 and a 62% inhibition of in vitro PNMT activity at concentrations of 10^{-4} M[14] vs. 100% inhibition for **21** at that concentration. These findings were further explored by the preparation and testing of **15**, a tertiary sulfonanilide. The additional information gained with this compound supported the earlier findings that an acidic hydrogen atom was important for potent inhibitory activity. The data from the aralkyl derivatives (**16**–**18**) (Table I), although not from a completely analogous series, support this argument. The results obtained with the phenacyl compounds **19** and **20** suggest that an acidic NH moiety, rather than simply an acidic hydrogen atom, may be essential for PNMT-inhibitory activity.

Compounds **2** and **6** (Table I), the two most potent compounds in the in vitro PNMT-inhibition assay, were tested in vivo in a 7-day mouse study. When administered at a dose of 100 mg/kg b.i.d., **6** was without effect, not altering the ratio of adrenal catecholamine levels from control values. Compound **2**, on the other hand, caused a marked loss in body weight on day 2 on the 100 mg/kg regimen and the study was discontinued. Consequently, **2** was retested at 25 mg/kg b.i.d., whereupon no changes in the epinephrine to norepinephrine ratio were noted. In a comparable assay, **21**, at doses of 50 and 100 mg/kg b.i.d., lowered epinephrine levels and the ratio of epinephrine to norepinephrine, while at 25 mg/kg only the ratio of epinephrine to norepinephrine was lowered (Table III).

Although **2** and **6** were more potent than **21**, as inhibitors of in vitro PNMT activity, neither showed any indication of having activity comparable to **21** in vivo. The reason(s) for this discrepancy is not readily apparent. Other studies in this area have yielded similar results;[2,7] compounds have been found with a high degree of in vitro activity, compounds for which no in vivo activity can be demonstrated. This may be due to a claimed "blood–adrenal barrier"[16] or to other more commonplace factors such as absorption, metabolism, distribution, and excretion.

Table III. PNMT Inhibition

treatment	dose, mg/kg[a]	epinephrine[b]	epinephrine[b] / norepinephrine
control		8.3 ± 0.9	1.6 ± 0.2
2	25	8.0 ± 0.4	1.4 ± 0.03
control		8.1 ± 0.7	2.4 ± 0.1
6	100	7.0 ± 0.7	2.1 ± 0.1
control		7.7 ± 0.7	2.6 ± 0.2
21	25	6.7 ± 0.5	1.7 ± 0.1[c]
	50	5.9 ± 0.3[d]	1.4 ± 0.1[e]
	100	5.8 ± 0.3[d]	1.2 ± 0.1[e]

[a] Drug doses are on a unit dose basis as the free base; see Experimental Section. [b] Animals are dosed with the drug or vehicle on a b.i.d. basis for 6-7 consecutive days. On the morning of the next day they are dosed again and 2 h later are sacrificed by decapitation. The adrenals are removed, weighed, and homogenized in 10 mL of 0.4 N perchloric acid. An aliquot of the extract is passed through an alumina column at pH 8.2-8.6. The catechol derivatives are then eluted with 0.2 M acetic acid. Epinephrine and norepinephrine are analyzed fluometrically by a trihydroxyindole procedure.[17] [c] $p \leq 0.01$. [d] $p \leq 0.05$. [e] $p \leq 0.001$.

Experimental Section

Melting points were determined in a Thomas-Hoover melting point apparatus or an electrically heated metal block (Mel-temp) and are uncorrected. Compounds for which formulas are given were analyzed for C, H, and N; analytical values were within ±0.4% of the calculated values unless otherwise noted. Analyses were performed by members of our Analytical and Physical Chemistry Section.

2-Acetyl-1,2,3,4-tetrahydroisoquinoline-7-sulfonanilides. A mixture of 23 g (0.07 mol) of crude 2-Ac-THIQ-7-SO_2Cl,[12,15] 0.09

(14) W. E. Bondinell and R. G. Pendleton, unpublished observations.

mol of substituted aniline, 110 mL of Me_2CO, and 14 mL of pyridine was stirred under reflux for 2 h. The excess solvents were removed and the residue was dissolved in $CHCl_3$. The $CHCl_3$ was washed successively three times with 3 N HCl, H_2O, 10% NaOH, and H_2O. The combined basic washes were extracted once with Et_2O and acidified with 3 N HCl. The resulting gum or solid was chilled and triturated. The product was collected, washed with H_2O, dried, and recrystallized.

7-Substituted 1,2,3,4-Tetrahydroisoquinoline Hydrochlorides (1–14 and 16–20). A mixture of 0.04 mol of 2-*N*-acyl derivative and 125 mL of 3 N HCl was stirred and heated to reflux. If solution was not obtained at reflux, dioxane was added cautiously until solution was effected. Heating was continued for 5–8 h. The solution was cooled and the solvent was evaporated. The residue was dried by azeotropic distillation with absolute EtOH. The resulting solid was collected, washed with Et_2O, and recrystallized.

7-*N*-(2,3-Dichlorophenyl)-1,2,3,4-tetrahydro-2-(trifluoroacetyl)isoquinoline-7-sulfonamide. THIQ (420 g, 2 mol) was stirred and cooled while 133 g (1 mol) of $(CF_3CO)_2O$ was added dropwise below 15 °C. The cooling bath was removed and stirring was continued for 3 h. The orange solution was heated and a mixture of TFA and $(CF_3CO)_2O$ was collected until the temperature of the distillate reached about 60 °C. At this point the residue was distilled at reduced pressure to give 210 g (92%) of 2-CF_3CO-THIQ boiling at 136–138 °C at 13 mmHg.

To a stirred solution of 172 g (0.75 mol) of 2-CF_3CO-THIQ in 2500 mL of $CHCl_3$, cooled to −10 °C, was added dropwise 326 mL of $ClSO_3H$. The addition required 2–3 h and was conducted below −5 °C. The solution was gradually allowed to come to room temperature and was then stirred for 60 h. The reaction mixture was added carefully with stirring in a very slow stream to 3 vol of ice–H_2O. The layers were separated and the aqueous phase was extracted with $CHCl_3$. The combined organic phases were washed with H_2O, dried, and evaporated. The residue was triturated with Et_2O to crystallize white solid weighing 106.5 g and melting at 101–102 °C.

On standing, the ethereal filtrate deposited several additional crops of solid that weighed 40 g, mp 84–100 °C. TLC of these crops on silica gel plates using $CHCl_3$ for development indicated these materials were predominantly the desired 2-CF_3CO-THIQ-7-SO_2Cl. An analytical sample was recrystallized from $CHCl_3$–Et_2O: mp 108–109 °C; MS *m/e* 327. Anal. ($C_{11}H_9ClF_3NO_3S$) C, H, Cl, N.

Conversion of the sulfonyl chloride to the sulfonanilide was as described above. Isolation was similar except that the product was not extracted into base. The acid-washed $CHCl_3$ solution was dried and evaporated, and the residue was triturated with Et_2O to induce crystallization. This intermediate was used to prepare **14**.

7-*N*-(*p*-Chlorophenyl)-7-*N*-methyl-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide Hydrochloride (15). A stirred solution of 7.5 g (0.02 mol) of 2-Ac-THIQ-7-SO_2NH-*p*-ClC_6H_4 in 100 mL of MeOH was treated with 1.4 g (0.025 mol) of NaOMe and 5 mL of MeI. The solution was stirred under reflux for 2 h and left at room temperature for 18 h. The mixture was concentrated and the residue was partitioned between H_2O and $CHCl_3$. The layers were separated and the aqueous phase (neutral) was extracted twice with $CHCl_3$. The organic phases were washed twice with 10% NaOH and H_2O, dried, and evaporated to give 7.9 g of viscous oil.

The oil was stirred under reflux for 3.5 h with 80 mL of 3 N HCl and was then left for 18 h at room temperature. The resulting precipitate was collected and recrystallized.

2-Acetyl-7-*N*-aralkyl-1,2,3,4-tetrahydroisoquinoline-7-sulfonamides. A solution of 19.2 g (0.07 mol) of 2-Ac-THIQ-7-SO_2Cl, 0.07 mol of aralkylamine, 14 mL of pyridine, and 140 mL of Me_2CO was stirred under reflux for 4–6 h. The red solution or mixture was cooled and filtered or concentrated.

The collected solid or gum was dissolved in $CHCl_3$ and the $CHCl_3$ was washed with 3 N HCl and H_2O, dried, and evaporated. The residue was crystallized or hydrolyzed without further purification.

2-Acetyl-7-[[β-(*p*-chlorophenyl)-β-oxoethyl]thio]-1,2,3,4-tetrahydroisoquinoline. A stirred solution of 27.3 g (0.1 mol) of crude 2-Ac-THIQ-7-SO_2Cl in 500 mL of HOAc was warmed to 75 °C, whereupon a solution of 100 g of $SnCl_2 \cdot 2H_2O$ in 90 mL of concentrated HCl was added. The solution was stirred at room temperature for 1.5–2 h. The solution was poured into 2 L of ice–H_2O containing 100 mL of 12 N HCl. The resulting mixture was filtered as quickly as possible under N_2. The sticky solid was washed with ice–H_2O and was suspended in 400 mL of MeOH. The suspension of crude 2-Ac-THIQ-7-SH was blanketed with N_2 and to it was added 6 g (0.11 mol) of NaOMe and 25 g (0.1 mol) of α-bromo-*p*-chloroacetophenone. The mixture was stirred at room temperature for 2 h under N_2 and was left standing for 18 h. The solvent was distilled in vacuo and the residue was distributed between H_2O and $CHCl_3$. The layers were separated and the aqueous phase was extracted with $CHCl_3$. The combined $CHCl_3$ phases were washed with H_2O, dried, and evaporated. The residual mixture was chromatographed on a column of Woelm neutral alumina, activity 1 (ICN Pharmaceuticals, Inc., Life Sciences Group, Cleveland, Ohio), using EtOAc–cyclohexane (3:2, v/v) for development. Fractions of 200 mL were collected and fractions 7–20 were combined and evaporated to give 8 g of crude product. Trituration of the residue with MeOH induced crystallization. Recrystallization from MeOH gave material melting at 104–106 °C.

2-Acetyl-7-[[β-(*p*-chlorophenyl)-β-oxoethyl]sulfonyl]-1,2,3,4-tetrahydroisoquinoline. A solution of 2.4 g (6 mmol) of the above thio compound, 3 g of *m*-chloroperoxybenzoic acid, and 50 mL of $CHCl_3$ was stirred at room temperature for 45 min. The solution was extracted with 5% Na_2CO_3 and with H_2O, dried, and evaporated. The residual foam was triturated with a small volume of MeOH, and the resulting solid was collected and recrystallized.

Biological Assays. In vitro PNMT assays (Table I) were performed using a partially purified, lyophilized PNMT preparation derived from rabbit adrenals. The enzyme preparation was obtained from Accurate Chemical Co., Hicksville, N.Y. The assays were carried out as reported previously[9,10,12] using (−)-norepinephrine as the methyl group accepting substrate. A compound was considered to show activity in this preparation at a molar concentration which produced at least a 30% inhibition of PNMT. A compound producing a 90% or greater inhibition of PNMT at 10^{-4} M or less was considered of significant interest for further study.

2 and **6** were tested in vivo in male Charles River mice. The compounds were administered orally in 1% methylcellulose in a dose volume of 10 mL/kg of body weight. The animals were dosed with the compounds b.i.d. for 6–7 consecutive days. On the morning of the next day they were dosed again and 2 h later were sacrificed by decapitation. The adrenals were removed, weighed, and homogenized in 10 mL of 0.4 N $HClO_4$. An aliquot of the extract was passed through an alumina column at pH 8.2–8.6 and the catechol derivatives were eluted with 0.2 M HOAc. The levels of epinephrine and norepinephrine were determined fluorimetrically by a trihydroxyindole procedure[17] (Table III).

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