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Inhibition of Adrenal Phenethanolamine-*N*-methyltransferase by Substituted Imidazoles

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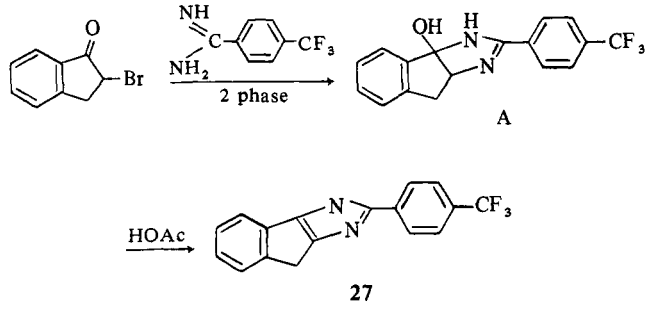
A series of substituted imidazoles was synthesized and tested for their inhibitory effect *in vitro* on bovine adrenal phenethanolamine-*N*-methyltransferase, the enzyme catalyzing the conversion of norepinephrine to epinephrine *in vivo*. The most potent *in vitro* inhibitors found were those substituted with Ph rings carrying electron-withdrawing groups. These compounds produced 27–81% inhibition of enzyme activity at 2.8 μg/ml and also produced small but measurable inhibition at 0.28 μg/ml. Several compounds active in the *in vitro* assay produced only a marginal (20%) inhibition of adrenal epinephrine biosynthesis when administered ip to mice and rats in 3 doses of 100 mg/kg per dose.

Phenethanolamine-*N*-methyltransferase (PNMT) catalyzes the final step in the biosynthesis of epinephrine in which a Me group is transferred from *S*-adenosylmethionine to the primary amine N of norepinephrine.[1] PNMT is highly localized in the adrenal medulla and is under the control of the pituitary-adrenocortical system.[2] PNMT is inhibited by several types of compounds including SH binding agents,[1] phenethylamines,[3] tranylcypromine, and other amines,[4] and substituted amphetamines.[5] We previously reported that certain substituted benzimidazoles were potent inhibitors of adrenal PNMT *in vitro* and that some of these compounds inhibited the formation of adrenal epinephrine when administered to mice and rats *in vivo*.[6] As an extension of this work several ring systems similar to the benzimidazoles were prepared and tested. Of these, the phenyl-substituted imidazoles (Table I) and the indenoimidazoles (Table II) showed the best activities in their inhibitory effect on PNMT *in vitro*. Several of these compounds were also evaluated for their ability to lower adrenal epinephrine levels *in vivo*.

Chemistry. The 4(5)-substituted phenyl imidazoles were prepared from α-bromoacetophenone and formamide,[7] while condensation of an α-aminoacetophenone and cyanamide[8] gave the 2-amino-4(5)-phenylimidazoles. The 2-phenylimidazoles were prepared by a method devised in these laboratories whereby the appropriate benzamidine is treated with aminoacetaldehyde diethyl acetal[9] (see preparation of **17**). The 2,4-bis(phenyl) compound **20** was prepared by a 2-phase condensation of a benzamidine and an α-bromoacetophenone.[10] This 2-phase system was also used in the preparation of indenoimidazole **27** and led to a number of products, but fortunately an OH intermediate assigned structure A (see Scheme I) could be isolated due to its insolubility and converted to the desired product by dehydration. The methylations of 4-phenyl-substituted imidazoles were carried out with Me_2SO_4 without solvent. As has been previously reported,[11] these conditions give predominantly (for **14** and **21** > 90%) the 1,4 derivative.†

Scheme I



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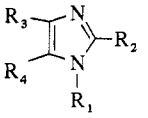
In Vitro **Methods.** PNMT was prepared from steer adrenal medullae and assayed according to the methods described in the previous publication.[6] Briefly, the partially purified enzyme was incubated with *S*-adenosylmethionine-*methyl*-^{14}C and normetanephrine in a phosphate buffer, pH 7.9, for 30–60 min at 37°. The metanephrine-^{14}C formed in the *in vitro* incubation was extracted into *i*-AmOH-PhMe and its radioactivity determined. In some experiments norepinephrine replaced normetanephrine as the substrate in the assay and the extraction procedure was modified.[1] The compounds evaluated in the present study and their melting points or a literature reference to their respective method of preparation

†Compd **8** was prepared according to ref 11a and its mp and that of its hydrobromide were the same as reported but the nmr spectrum of our sample still showed 8% of the 1,5 isomer.

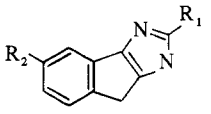
Table I. Imidazole Derivatives



No.	R_1	R_2	R_3	R_4	Mp, °C and/or ref	Formula
1	H	H	H	H	*a*	
2	H	H	CH_3	CH_3	*b*	
3	H	H	$CH_2CH_2NH_2$	H	*a*	
4	H	H	Ph	H	*a*	
5	H	Ph	H	H	*a*	
6	H	H	Ph	Ph	*a*	
7	H	Ph	Ph	Ph	*a*	
8	H	NH_2	Ph	H	*c*	
9	CH_3	H	Ph	H	109–111[d]	
10	H	H	*p*-CF_3Ph	H	151–151.5	$C_{10}H_7F_3N_2$[g]
11	H	NH_2	*p*-CF_3Ph	H	170–173	$C_{10}H_8F_3N_3$[g]
12	H	SCH_3	*p*-CF_3Ph	H	180.5–182	$C_{11}H_9F_3N_2S$[g]
13	H	SH	*p*-CF_3Ph	H	270–280 dec	$C_{10}H_7F_3N_2S$[g]
14	CH_3	H	*p*-CF_3Ph	H	145–146	$C_{11}H_9F_3N_2$[g]
15	H	*p*-ClPh	H	H	*e*	
16	H	*p*-FPh	H	H	*e*	
17	H	*p*-CF_3Ph	H	H	238–241	$C_{10}H_7F_3N_2$[g]
18	H	3,4-$Cl_2C_6H_3$	H	H	*e*	
19	CH_3	*p*-CF_3Ph	H	H	115.5–117.5	$C_{11}H_9F_3N_2$[g]
20	H	*p*-CF_3Ph	*p*-CF_3Ph	H	190–192	$C_{17}H_{10}F_6N_2$[g]
21	CH_3	*p*-CF_3Ph	*p*-CF_3Ph	H	89–93	$C_{18}H_{12}F_6N_2$[g]
22	CH_3	H	NO_2	Cl	*f*	

[a]Commercially available. [b]See ref 7. [c]See ref 8. [d]See ref 11a. [e]See ref 9. [f]See ref 12. [g]Analyzed for C, H, N.

Table II.



No.	R_1	R_2	Mp, °C	Formula[a]
23	H	H	168–172	$C_{10}H_8N_2$
24	H	Cl	198–201.5	$C_{10}H_7ClN_2$
25	SCH_3	H	166–168	$C_{11}H_{10}N_2S$
26	SCH_3	Cl	219–223	$C_{11}H_9ClN_2S$
27	*p*-CF_3Ph	H	206–211	$C_{17}H_{11}F_3N$

[a]Analyzed for C, H, N.

are listed in Tables I and II. The ability of the substituted imidazoles to inhibit the methylation of normetanephrine by *S*-adenosylmethionine and partially purified steer adrenal PNMT is shown in Table III.

In Vitro **Results.** As in the case of the benzimidazoles[6] it was found that introduction of an electron-withdrawing group in the phenylimidazoles or indenoimidazoles greatly increases activity (*cf.* **4** *vs.* **10**, **9** *vs.* **14**, and **23** *vs.* **24**). The most potent of these compounds, **20**, and its more lipophilic derivative, **21**, were almost as potent in inhibiting methylation of normetanephrine (Table III) as the more potent benzimidazoles.[6] Some of the compounds were also tested for inhibitory effects on the methylation of norepinephrine (Table III), the substrate considered to be the one occurring *in vivo*.[3] In general, the compounds were somewhat less active when 6×10^{-5} *M* DL-norepinephrine was substituted for 5.7×10^{-4} *M* DL-normetanephrine in the assay.

When compared to the substituted benzimidazoles, the imidazoles are a less potent class of PNMT inhibitors. To date, the substituted benzimidazoles remain the most potent class of compounds known to inhibit PNMT activity *in vitro*.

In Vivo **Studies.** A limited number of compounds were tested *in vivo* for their effect on adrenal epinephrine levels. The procedures for the *in vivo* administration of the compounds and the methodology for the measurement of catecholamines were described previously.[6] Most of the compounds were administered ip in 3 doses of 100 mg/kg each during 24 hr; compd **8** was given at 25 mg/kg because of toxicity. None of the compounds markedly lowered adrenal epinephrine. Those inhibitors which yielded a ratio [(adrenal epinephrine/adrenal norepinephrine)$_{\text{treated animal}}$: (adrenal epinephrine/adrenal norepinephrine)$_{\text{control animal}}$] of 0.8 may be considered active. As shown in Table IV, **8**, **14**, **15**, and **18** are inactive *in vivo*. Compd **17** is marginally active in both mice and rats and **20** is marginally active in rats but inactive in mice. Compds **14**, **17**, and **20** were also evaluated orally in rats in a 5-dose protocol (100 mg/kg per dose) over 48 hr; all 3 compounds produced a 23% reduction in adrenal epinephrine. Thus, in contrast to the substituted benzimidazoles, the imidazole derivatives are less active as inhibitors of the biosynthesis of adrenal epinephrine *in vivo*.[6] Because of the limited number of compounds tested *in vivo* and their lack of substantial activity in the animals, no relationship between activity *in vivo* and potency as enzyme inhibitors *in vitro* could be established.

Like the benzimidazole derivatives, the substituted imidazoles produced toxicity in the animal experiments. Compds **14**, **17**, and **20** were studied more thoroughly in rats and at doses of 100 mg/kg × 3, ip, anorexia and weight loss was noted. Compds **14** and **17** produced sedation and **17** and **20** also produced some adrenal hemorrhage. Compds **17** and **20** were apparently poorly absorbed when administered ip, since small amounts of these compounds were found in the peritoneal cavity upon sacrificing the animals. Thus far, *in vivo* studies with the substituted benzimidazole or imidazole series have not revealed a potent PNMT inhibitor which is completely devoid of side effects.

Table III. Inhibition of Adrenal Phenethanolamine-*N*-methyltransferase *in Vitro*

No.	Concn, μg/ml	% inhibition of the methylation of: 5.7×10^{-4} *M* DL-normetanephrine	% inhibition of the methylation of: 6.0×10^{-5} *M* DL-norepinephrine
1	28	14	
2	28	0	
3	28	0	
4	28	0	
5	28	0	
6	28	30	
7	28	0	
8	28	25	
9	28	27	
10	28	50	
11	28	16	
12	28	18	
13	28	0	
14	28	84	45
	2.8	45	19
15	28	70	64
16	28	30	
17	28	92	73
	2.8	59	26
	0.28	15	
18	28	87	65
	2.8	40	20
19	28	10	
20	28	92	63
	2.8	75	45
	0.28	28	
21	28	83	69
	2.8	81	47
	0.28	31	
22	28	58	
23	28	43	
24	28	74	
	2.8	36	
	0.28	17	
25	28	70	30
	2.8	33	35
26	28	69	
	2.8	27	
	0.28	0	
27	28	19	

Table IV. Inhibition of Adrenal Epinephrine Formation *in Vivo*

No.	Test animal	Dosage, mg/kg × 3 doses	Activity[a]
8	Mouse	25	0.84
14	Mouse	100	0.98
	Rat	100	0.93
15	Mouse	100	0.88
17	Mouse	100	0.80
	Rat	100	0.82
18	Mouse	100	0.87
20	Mouse	100	0.96
	Rat	100	0.80

[a] $\frac{(\text{adrenal epinephrine/adrenal norepinephrine})_{\text{treated animal}}}{(\text{adrenal epinephrine/adrenal norepinephrine})_{\text{control animal}}}$

Experimental Section‡

4-Trifluoromethylbenzimidic Acid Ethyl Ester·HCl. A mixt of 17.1 g of *p*-trifluoromethylbenzonitrile and 25 ml of abs EtOH was stirred and cooled with an ice bath before 75 ml of EtOH which had been cooled to 0° and satd with dry HCl was added. After 4 days at 5°, the soln was concd *in vacuo* to a slush and Et_2O was added to ppt successive crops totaling 23.8 g, mp 185–186°. *Anal.* ($C_{10}H_{11}ClF_3NO$) H, N, C: calcd, 47.35; found, 46.84.

‡Melting points were detd on a Kofler hot stage and are corr. Compounds were routinely examined by ir and nmr spectroscopy and tlc. Where analysis are indicated only by symbols of the elements analytical results obtained for those elements were within ±0.4% of the theoretical values.

4-Trifluoromethylbenzamidine·HCl. A 7.5-g portion of 4-trifluoromethylbenzamidic acid Et ester·HCl was dissolved in 40 ml of abs EtOH and a ~5% soln of NH_3–EtOH was added ~1 ml at a time with stirring until the odor of NH_3 persisted. After standing 2 days the soln was concd to a solid which was washed well with Et_2O to give 6.7 g of product which was used without further purification.

4(5)-(4-Trifluoromethylphenyl)imidazole (10). A mixt of 3.00 g of 2-bromo-4′-trifluoromethylacetophenone[13] and 15 ml of $HCONH_2$ was heated at 155° for 2 hr in a flask fitted with a Vigreux column. After cooling the mixt the reaction mixt was poured into 60 ml of boiling 1.25 *N* HCl contg activated charcoal. After filtration the filtrate was cooled in an ice bath and made pH 8.0 with NH_4OH. Collection of the ppt gave 1.49 g of crude product, mp 122–142°. Purification was achieved by sublimation [120° (600 μ)] and recrystn from C_6H_6.

2-Amino-4(5)-(4-trifluoromethylphenyl)imidazole (11). To a mixt of 2.0 g of 2-amino-4′-(trifluoromethyl)acetophenone·HCl,[13] 23 ml of H_2O, 0.2 ml of HOAc, and 2.1 g of 50% H_2NCN were added 3.4 ml of 2.5 *N* NaOH and 1 ml of HOAc, and the mixt was heated 1 hr on a steam bath. After cooling the ppt was collected and slurried with excess dil NaOH to yield 1.38 g of crude product, mp 115–168°. Sublimation [140° (75 μ)] gave pure product.

2-Methylthio-4(5)-(4-trifluoromethylphenyl)imidazole (12). To a soln of 0.50 g of **13** in 25 ml of MeOH was added 0.82 ml of 2.5 *N* NaOH. The mixt was concd *in vacuo* to a solid which was redissolved in 10 ml of MeOH and refluxed 3 hr with 130 μl of CH_3I. Concn *in vacuo* gave a yellow solid to which was added 10 ml of H_2O and NH_4OH to adjust the pH to 10.5. Collection of the solid gave 0.48 g of crude product. Two recrystns from $CHCl_3$ gave pure product.

2-Mercapto-4(5)-(4-trifluoromethylphenyl)imidazole (13). A mixt of 4.0 g of 2-amino-4′-trifluoromethylacetophenone·HCl,[13] 1.64 g of KSCN, and 50 ml of HOAc was refluxed 10 min. After cooling, 2.06 g of crude product was collected on a filter. Addn of 20 ml of H_2O to the filtrate pptd 1.35 g of a second crop which was recryst from HOAc to yield analytical material.

1-Methyl-4-(4-trifluoromethylphenyl)imidazole (14). A mixt of 53.3 g of **10** and 26 ml of $(CH_3)_2SO_4$ was heated on a steam bath for 25 min, cooled, and added to 1.5 l. of H_2O. The pH was adjusted to 10 with 10% NaOH and the mixt was extd with $CHCl_3$. The $CHCl_3$ layers were dried with Na_2SO_4 and concd *in vacuo*. The residue was extd with Et_2O and the Et_2O-soluble fraction chromatographed on silica gel using 6% MeOH–$CHCl_3$ as eluant. The product thus sepd from starting material was recrystd from Et_2O, 11 g.

2-(4-Trifluoromethylphenyl)imidazole (17). A 59-g portion of 4-trifluoromethylbenzimidic acid Et ester·HCl was stirred in 142 ml of MeOH and 33.8 g of aminoacetaldehyde diethyl acetal in 102 ml of MeOH was added dropwise with stirring as the temp was maintained at ~5°. After stirring 15 hr at room temp the mixt was concd to 100 g of viscous oil which was treated dropwise at 20–25° with 83 ml of concd H_2SO_4. After stirring 15 hr at room temp, the mixt was poured into ice H_2O and neutralized with 450 ml of 50% NaOH. The crude solid was collected and recrystd from C_6H_6 to give 22 g of pure product.

1-Methyl-2-(4-trifluoromethylphenyl)imidazole (19). A 0.65-g portion of 2-(4-trifluoromethylphenyl)imidazole (**17**) was heated 5 min on a steam bath with 0.58 g of Me_2SO_4. After cooling the brown oil was triturated with excess dil NaOH and the resultant yellow solid was purified by preparative tlc on 3 × 1000 μ silica gel G plates (8% MeOH–$CHCl_3$) to give 136 mg of product. The material was sublimed [135° (50 μ)] for analysis.

2,4(5)-Bis(4-trifluoromethylphenyl)imidazole (20). A 2-phase mixt of 3.2 g of 2-bromo-4′-trifluoromethylacetophenone[13] in 23 ml of $CHCl_3$ and 2.54 g of 4-trifluoromethylbenzamidine·HCl in 15 ml of H_2O was stirred and a soln of 1.5 g of KOH in 15 ml of H_2O was added. After stirring and refluxing 3 hr, the mixt was cooled and the layers were sepd. The $CHCl_3$ layer was combined with $CHCl_3$ washings of the aqueous layer, dried ($MgSO_4$), and concd *in vacuo* to a residue which was recrystd from C_6H_6 to give 1.89 g of product, mp 188–191°. An analytical sample was obtained by recrystn from C_6H_6 followed by sublimation [150° (50 μ)].

1-Methyl-2(4)-bis(4-trifluoromethylphenyl)imidazole (21). A 178-mg portion of **20** and 0.08 ml of Me_2SO_4 were mixed and heated on a steam bath for 10 min. After cooling the mixt was taken up in $CHCl_3$ and dil NaOH. The organic layer was sepd, dried (Na_2SO_4), and concd to 217 mg of oil which was chromatographed on silica gel plates (4% MeOH–$CHCl_3$) to give 70 mg of product, mp 90–92°. An analytical sample was obtained by sublimation.

Indeno[1,2-*d*]imidazole (23). A 1.00-g portion of 2-mercaptoindeno[1,2-*d*]imidazole[14,§] and 7–8 g of RaNi were stirred and refluxed in 30 ml of EtOH for 1 hr. While still hot the mixt was fil-

tered to remove the RaNi which was washed with 3 ×10 ml of EtOH. The filtrate and washings were concd to 0.47 g of pale green crude product which was purified by sublimation [120° (100–200 μ)].

6-Chloro-1-indanone.[15] A mixt of 35 g of *p*-chlorohydrocinnamic acid[16] and 414 g of polyphosphoric acid was heated on a steam bath for 0.5 hr. Diln with 3 l. of H_2O gave a ppt which was dissolved in Et_2O. The Et_2O soln was washed with $NaHCO_3$, steam distd, and the steam-distd material recrystd from EtOH to give 9.5 g of material melting at 70–73° which was >95% pure by tlc.

6-Chloro-2-isonitroso-1-indanone. A soln of 5.7 g of 6-chloro-1-indanone in 60 ml of C_6H_6 was stirred and HCl gas was bubbled in as 4.8 g of *i*-AmONO was added dropwise over a period of 15 min. Addn of HCl was contd 20 min longer and the mixt was stirred 15 hr before 2.6 g of product was collected, mp 200–204° dec. Resubmission of the mother liquors gave 1.3 g of addnl product. *Anal.* ($C_9H_6ClNO_2$) C, H, N, Cl.

2-Amino-5-chloro-1-indanone·HCl. To a stirred mixt of 9.13 g of $SnCl_2 \cdot 2H_2O$ in 13 ml of concd HCl was added portionwise 3.6 g of 6-chloro-2-isonitroso-1-indanone over a period of 1.5 hr. The temp was kept <40° with intermittent cooling. After stirring 0.5 hr at room temp and 0.5 hr at 95°, the mixt was cooled and 500 ml of H_2O was added. The mixt was stirred and H_2S was bubbled in until no further ppt was obtained. Solids were removed by filtration and concn of the filtrate gave 1.5 g of crude product. Purification for analysis was achieved by recrystn from MeOH–Et_2O, mp 195–210° dec. *Anal.* ($C_9H_9Cl_2NO$) C, H, N, Cl.

5(7)-Chloro-2-mercapto-1,4(8)-dihydroindeno[1,2-*d*]imidazole. A mixt of 1.44 g of 2-amino-5-chloro-1-indanone·HCl and 0.675 g of KSCN were refluxed 15 min in 45 ml of glacial HOAc. After cooling, 0.60 g of crude product was collected on a filter and was used without further purification, mp >300°.

5(7)-Chloro-1,4(8)-dihydroindeno[1,2-*d*]imidazole (24). A 310-mg portion of crude 5(7)-chloro-2-mercapto-1,4(8)-dihydroindeno-[1,2-*d*]imidazole was treated with RaNi as in the prepn of **23** to give 106 mg of crude product which was purified by prep tlc (10% MeOH–$CHCl_3$ on silica gel G) followed by trituration with Et_2O. This gave 35 mg of product: mass spectrum (70 eV) *m/e* 190 (base peak).

2-Methylthioindeno[1,2-*d*]imidazole (25). To a slurry of 1.88 g of 2-mercaptoindeno[1,2-*d*]imidazole in 50 ml of THF was added 0.70 ml of MeI. After 16 hr of stirring the ppt was collected and stirred with excess 1 *N* NaOH. Collection of the ppt gave 1.11 g of product.

5(7)-Chloro-2-methylthio-1,4(8)-dihydroindeno[1,2-*d*]imidazole (26). A 0.31-g portion of crude product was heated with MeI as described in the prepn of **25** to yield 70 mg of crude product, mp 217–223°. This material was purified by sublimation at 150° (50 μ): mass spectrum (70 eV) *m/e* 236 (base peak).

§ Prepared in HOAc according to procedure of Norris and McKee.[14b]

2-(4-Trifluoromethylphenyl)-1,4(8)-dihydroindeno[1,2-*d*]imidazole (27). A mixt of 3.24 g of 2-bromo-1-indanone[17] in 30 ml of $CHCl_3$ and 3.30 g of 4-trifluoromethylbenzamidine·HCl in 10 ml of H_2O was stirred vigorously and 1.8 g of KOH in 10 ml of H_2O was added. The mixt was stirred and refluxed for 3 hr before the resultant ppt was collected and washed with H_2O and $CHCl_3$ to give 0.80 g of intermediate OH compd with a strong *m/e* of 340. A 0.70-g portion of this intermediate was refluxed 10 min in 7 ml of HOAc. The HOAc was removed *in vacuo* and the residue extd with 10 ml of Et_2O. The Et_2O ext was concd to 0.58 g of crude product which was recrystd 4 times from MeOH to give 0.27 g of pure product.

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Lowering of Serum Lipid Levels by "Masked" Nicotinic Acid Derivatives

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A series of "masked" nicotinic acid compounds (acyl derivatives of 3-pyridylmethylamines, nicotinic acid hydrazides, and nicotinohydroxamic acids) has been synthesized. These compounds have been evaluated with rats orally for their ability to reduce serum NEFA levels and parenterally to reduce serum cholesterol and triglyceride levels. The effective hypolipemic doses of the test compounds were roughly equivalent on a molar basis to those of the parent nicotinic acid. The peripheral vasodilating (flushing) or gastric secretion stimulating effects of these compounds appeared not to differ meaningfully from nicotinic acid.

Prophylactic and therapeutic efforts to control atherosclerosis in man have focused on the control of blood lipid levels. Nicotinic acid (NA), a clinically effective hypolipemic agent, decreases (1) nonesterified fatty acid (NEFA) release from the liver, (2) NEFA and glycerol levels in plasma, (3) liver uptake of circulating NEFA, and (4) hepatic triglyceride synthesis.[1] Its use, however, has been fraught with complications due to disturbances of liver function,[2,3] carbohydrate metabolism,[4–6] gastrointestinal distress,[7,8] and flushing.[9]

An interim report on a large-scale survey from the VA