New Sedative and Hypotensive Phenylpiperazine Esters and Carbamates

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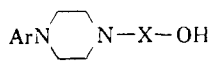
A number of N-(4-aryl-1-piperazyl)alkyl polymethoxybenzoates and N-substituted (4-aryl-1-piperazyl)alkyl carbamates were prepared.

The presence of the 3,4,5-trimethoxybenzoic acid ester group in reserpine has led to numerous studies of the pharmacological properties of polymethoxybenzoic acid esters of substituted amino alcohols.[1] This paper describes the synthesis of a number of polymethoxybenzoates and N-substituted carbamates of 4-aryl-1-piperazylalkanols as potential psychosedative agents.

4-Aryl-1-piperazylalkanols (Table I) were prepared by treating the appropriate N-arylpiperazine with ethylene oxide or ω-haloalkanols. 4-Phenyl-1-(5-hydroxypentyl)piperazine was obtained in high yield by treating 1-phenylpiperazine with 2-hydroxytetrahydropyran, and then catalytic hydrogenolysis.[2]

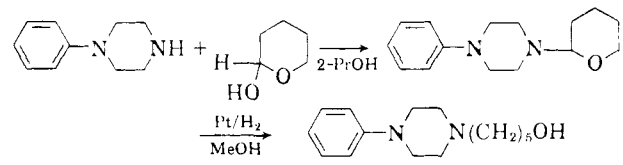
TABLE I

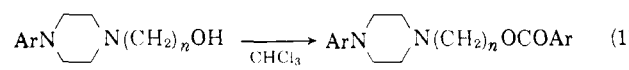


Ar	X	Formula	M.p., °C.	Nitrogen, %[a] Calcd.	Found
C_6H_5	$(CH_2)_2$	$C_{12}H_{18}N_2O$	84–85[d]	6.80	6.77
4-$CH_3OC_6H_4$	$(CH_2)_2$	$C_{13}H_{20}N_2O_2$	92–93[e]	5.93	5.86
4-ClC_6H_4	$(CH_2)_2$	$C_{12}H_{17}ClN_2O$	109–111[f]	5.82	5.89
C_6H_5	$CH_2CH(CH_3)$	$C_{13}H_{20}N_2O$	76–78[g]	..	..
C_6H_5	$(CH_2)_3$	$C_{13}H_{20}N_2O^h$		12.7	12.9[b]
		$C_{13}H_{22}Cl_2N_2O$	216–217	4.78	4.80
4-$CH_3OC_6H_4$	$(CH_2)_3$	$C_{14}H_{22}N_2O_2$	88–91.5	5.60	5.20
4-ClC_6H_4	$(CH_2)_3$	$C_{13}H_{19}ClN_2O$	107–109	5.50	5.84
C_6H_5	$(CH_2)_4$	$C_{14}H_{22}N_2O$	65–68[i]	5.98	5.88
4-ClC_6H_4	$(CH_2)_4$	$C_{14}H_{21}ClN_2O$	79–81	5.22	5.59
C_6H_5	$(CH_2)_5$	$C_{15}H_{24}N_2O$	78–78.5[j]	5.64	5.62
		$C_{15}H_{26}Cl_2N_2O$	195–196	22.7	22.6[c]

[a] Basic nitrogen by titration with $HClO_4$. [b] Total nitrogen (Kjeldahl). [c] Hydrogen chloride by titration with NaOH. [d] M.p. 91°, V. Prelog and Z. Blazek, *Collection Czech. Chem. Commun.*, **6**, 549 (1934). [e] M.p. 88°, W. Davis and W. C. J. Ross, *J. Chem. Soc.*, 2831 (1949). [f] M.p. 107–108.5°, C. B. Pollard and T. H. Wicker, *J. Am. Chem. Soc.*, **76**, 1853 (1954). [g] G. B. Bachman and R. J. Mayhew, *J. Org. Chem.*, **10**, 243 (1945). [h] M.p. 73°, Soc. us. chim. Rhône-Poulenc, British Patent 807,750 (1959). [i] M.p. 59–60°, G. W. Anderson and C. B. Pollard, *J. Am. Chem. Soc.*, **61**, 3439 (1939). [j] M.p. 74–75°, ref. *i*.

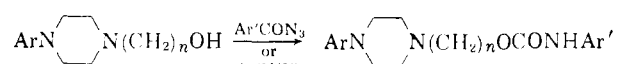
The esters in Table II were prepared by treating the alkanols with acid chlorides in chloroform (equation 1). All the esters were isolated as dihydrochlorides.





Ar = C_6H_5, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, 4-ClC_6H_4; Ar′ = 4-CH_3OC$_6$H$_4$, 3,4-$(CH_3O)_2C_6H_3$, 3,4,5-$(CH_3O)_3C_6H_2$, 3,4-$(CH_2O_2)C_6H_3$; n = 2,3,4,5

The compounds in Table III were prepared by reaction of the appropriate 4-aryl-1-piperazylalkanol with an isocyanate or acid azide (equation 2). The intermediate isocyanate required for the piperonyl derivatives was prepared by Siefken's method[3] in which phosgene is passed into a suspension of the amine hydrochloride in hot chlorobenzene. The carbamates formed dihydrochlorides, monomaleates, 1-methiodides[4] or oxalates.



(2)

Ar = C_6H_5, 4-$CH_3C_6H_4$; Ar′ = 4-$CH_3OC_6H_4$, 3,4-$(CH_3O)_2C_6H_3$, 3,4,5-$(CH_3O)_3C_6H_2$, 3,4-$(CH_2O_2)C_6H_3$ and 3,4-$(CH_2O_2)C_6H_3CH_2$; n = 2,3,4,5

Pharmacology.—Many of the compounds of both groups are antiadrenergic agents; on intravenous administration they reverse or block the pressor response to epinephrine and partially block the response to norepinephrine. Upon intravenous administration in the pentobarbitalized dog, they produce a sustained hypotension, but in the normal unanesthetized dog the hypotensive effect of orally administered drug is uncertain and variable.

The esters were screened for sedative activity according to the method of Lim, *et al.*[5] A percentile scoring system was used for measuring eye closure, posture and spontaneous motor activity in rats. The median oral sedative dose for the most potent ester (VIII) is 4% of the A-LD_{50} (100 mg./kg.). Loss of righting reflex is seen at lethal doses. The oral median motor relaxation dose, as measured by the method of Dunham and Miya,[6] is 14% of the A-LD_{50} (347 mg./kg.). Its median effective convulsive facili-

(1) (a) R. A. Robinson, U. S. Patent 2,852,520 (1958); (b) W. Voegtli, U. S. Patent 2,907,764 (1959); (c) G. DiPaco and C. S. Tauro, *Farmaco* (Pavia) *Ed. Sci.*, **13**, 64, 429 (1958); (d) H. G. Moren, Belg. Patent 557,030 (1957); (e) J. Supniewski, K. Bednarz, and J. Krupinska, *Dissertations Pharm.* (Poland), **10**, 191 (1958); *Chem. Abstr.*, **53**,7435c (1959); (f) V. M. Solovév, A. P. Arendarruk, and A. P. Skoldinov, *Zh. Obshch. Khim.*, **29**, 613 (1959); (g) R. Ratouis and G. Combes, *Bull. soc. chim. France*, 576 (1959); (h) E. Cerkovnikov and P. Štern, *Arkiv Kemi*, **18**, 24 (1946); *Chem. Abstr.*, **42**, 1938e (1948); (i) G. Polazzo, L. Bizzi, and C. Pozzatti, *Proc. Intern. Congr. Neuro-Pharm.*, 1st, Rome, **1958**, 378 (1959); *Ann. chim.* (Rome), **49**, 853 (1959); *Chem. Abstr.*, **54**, 24510 (1960); (j) M. Protiva and Z. J. Vejdělek, Czech. Patent 94,243 (1960); *Chem. Abstr.*, **54**, 24799 (1960); (k) F. M. Miller and M. S. Weinberg, *Abstr. from 130th Am. Chem. Soc. Natl. Meeting*, 11-N (1956); (l) T. Kralt, H. D. Moed, V. Claassen, Th. W. J. Hendriksen, A. Lindner, H. Selzer, F. Brucke, G. Hertting, and G. Gogolak, *Nature*, **188**, 1108 (1960); (m) A. H. Sommers, U. S. Patent 2,891,063 (1959).

(2) C. Glacet and F. Blanchard-Bielli, *Compt. rend.*, **247**, 1467 (1958).

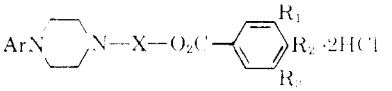
(3) W. Siefken, *Ann.*, **562**, 101 (1949).

(4) 1-(4-Carbamoyloxy)butyl-4-phenylpiperazine formed a monomethiodide, m.p. 163°. Strong absorption at 1600 cm.$^{-1}$ in the infrared and typical phenylpiperazine type absorption in the ultraviolet spectrum at 243 and 284 mμ (ε 19,000 and 1,800) showed that quaternization took place at the 1-position only.

(5) R. K. S. Lim, M. H. Pindell, H. G. Glass, and K. Rink, *Ann. N. Y. Acad. Sci.*, **64**, 667 (1956).

(6) N. W. Dunham and T. S. Miya, *J. Am. Pharm. Assoc.* (Sci. Ed.), **46**, 208 (1957).

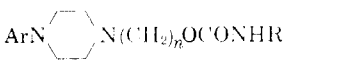
TABLE II



No.	Ar	X	R_1	R_2	R_3	Formula	M.p., °C.	Hydrogen chloride, % Calcd.	Found
I	C_6H_5	$(CH_2)_2$	OCH_3	OCH_3	OCH_3	$C_{22}H_{30}Cl_2N_2O_5$	188–190	15.4[b]	15.3
II	4-ClC_6H_4	$(CH_2)_2$	OCH_3	OCH_3	OCH_3	$C_{22}H_{29}Cl_3N_2O_5$	194–194.5	14.4	14.4
III	4-$CH_3OC_6H_4$	$(CH_2)_2$	OCH_3	OCH_3	OCH_3	$C_{23}H_{32}Cl_2N_2O_6$	205–206	14.5	14.5
IV	C_6H_5	$CH_2CH(CH_3)$	OCH_3	OCH_3	OCH_3	$C_{23}H_{32}Cl_2N_2O_5$	202–204	15.0[c]	15.1
V	C_6H_5	$(CH_2)_3$	OCH_3	OCH_3	OCH_3	$C_{23}H_{32}Cl_2N_2O_5$	180–181	..	..[a]
VI	4-ClC_6H_4	$(CH_2)_3$	OCH_3	OCH_3	OCH_3	$C_{23}H_{31}Cl_3N_2O_5$	187–188	14.0	13.8
VII	4-$CH_3OC_6H_4$	$(CH_2)_3$	OCH_3	OCH_3	OCH_3	$C_{24}H_{34}Cl_2N_2O_6$	203–204	14.6	14.8
VIII	C_6H_5	$(CH_2)_4$	OCH_3	OCH_3	OCH_3	$C_{24}H_{34}Cl_2N_2O_5$	194–196	14.6[d]	14.8
IX	C_6H_5	$(CH_2)_4$	OCH_3	OCH_3	H	$C_{23}H_{32}Cl_2N_2O_4$	184–185	15.5	15.8
X	C_6H_5	$(CH_2)_4$	H	OCH_3	H	$C_{22}H_{30}Cl_2N_2O_3$	210–211	16.6	16.9
XI	C_6H_5	$(CH_2)_4$	O—CH_2—O		H	$C_{22}H_{28}Cl_2N_2O_4$	215–218	16.0	16.3
XII	C_6H_5	$(CH_2)_5$	OCH_3	OCH_3	OCH_3	$C_{25}H_{36}Cl_2N_2O_5$	190–192	14.2	14.2

[a] Calcd. N, 5.75. Found: N, 5.62 (total nitrogen by Kjeldahl in *a*, *b*, *c*, and *d*). [b] Calcd. N, 5.92. Found: N, 5.93. [c] Calcd. N, 5.75. Found: N, 5.85. [d] Calcd. N, 5.59. Found: N, 5.80, 5.81.

TABLE III



No.	Ar	n	R	Formula	M.p., °C.	Nitrogen, %[a] Calcd.	Found
XIII	C_6H_5	2	4-$CH_3OC_6H_4$	$C_{20}H_{27}Cl_2N_3O_3$[e]	212.5–213 dec.	16.6	16.5[b]
XIV	C_6H_5	2	3,4-$(CH_3O)_2C_6H_3$	$C_{25}H_{31}N_3O_8$[c]	144.5–145.5	8.38	8.44
XV	C_6H_5	2	3,4-$(CH_2O_2)C_6H_3$	$C_{24}H_{27}N_3O_8$[c]	151–153	8.66	8.72
XVI	C_6H_5	2	3,4,5-$(CH_3O)_3C_6H_2$	$C_{24}H_{31}N_3O_9$[d]	155–156	8.32	8.24
XVII	4-$CH_3C_6H_4$	3	4-$CH_3OC_6H_4$	$C_{26}H_{33}N_3O_7$[c]	149.5–150.5	8.41	8.38
XVIII	C_6H_5	3	3,4,5-$(CH_3O)_3C_6H_2$	$C_{27}H_{35}N_3O_9$[c]	163–164 dec.	7.70	7.86
XIX	C_6H_5	4	3,4-$(CH_2O_2)C_6H_3$	$C_{26}H_{31}N_3O_8$[c]	157–159	8.19	8.21
XX	C_6H_5	4	3,4,5-$(CH_3O)_3C_6H_2$	$C_{28}H_{37}N_3O_9$[c]	152.5–154	7.51	7.58
XXI	C_6H_5	5	4-$CH_3OC_6H_4$	$C_{27}H_{35}N_3O_7$[c]	175–176.5 dec.	8.19	8.08
XXII	C_6H_5	5	3,4,5-$(CH_3O)_3C_6H_2$	$C_{29}H_{39}N_3O_9$[c]	132–133	7.33	7.38
XXIII	C_6H_5	2	3,4-$(CH_2O_2)C_6H_3CH_2$	$C_{25}H_{29}N_3O_8$[c]	108–109	8.42	8.59
XXIV	C_6H_5	3	3,4-$(CH_2O_2)C_6H_3CH_2$	$C_{22}H_{29}Cl_2N_3O_4$[c]	188–189 dec.	15.1	14.9[b]
XXV	C_6H_5	4	3,4-$(CH_2O_2)C_6H_3CH_2$	$C_{23}H_{31}Cl_2N_3O_4$[c]	194–194.5 dec.	14.7	14.5[b]
XXVI	C_6H_5	5	3,4-$(CH_2O_2)C_6H_3CH_2$	$C_{24}H_{33}Cl_2N_3O_4$[c]	178–178.5 dec.	14.3	14.2[b]

[a] Total nitrogen by Kjeldahl. [b] Chloride ion by titration. [c] Maleate. [d] Oxalate. [e] Dihydrochloride.

tation dose in rats is 7% of the A-LD_{50} (174 mg./kg.). This test is based on the production of hind limb tonic extension in drug-treated rats after administration of a subthreshold electroconvulsive stimulus. Compound VIII does not produce loss of righting reflex in rats after intraperitoneal administration of a subthreshold dose of sodium hexobarbital. Chronic studies[7] indicate that VIII does not produce cumulation or tolerance in rats and dogs. The compound is currently being evaluated clinically; early reports indicate that it is effective as a tranquilizer.

In the carbamate series, compound XVIII produces minimal sedative effects at 27 mg./kg. (3% A-LD_{50}) orally in rats. The sedative action was determined by gross observation of the exploratory behavior of rats.[8] At 36 mg./kg. intraperitoneally, compound XVIII affords 100% protection against *d*-amphetamine sulfate (15 mg./kg. i.p.) toxicity[9] in grouped mice (10 mice/group). This compound is being prepared for clinical trial.

The detailed pharmacology will be published elsewhere.

Experimental[10]

1-Phenyl-4-(5-hydroxypentyl)piperazine.—To a solution of 1-phenylpiperazine (32.4 g., 0.2 mole) in 150 ml. of 2-propanol was added 2-hydroxytetrahydropyran (22.5 g., 0.22 mole) all at once; the clear solution gave a colorless solid in a few min. It kept at room temperature overnight and the solid, 1-phenyl-4-(2-tetrahydropyranyl) piperazine, was collected, washed with 2-propanol and air dried; yield 37.1 g. (74.5%). A sample was recrystallized once from Skelly B to give a sandy solid of m.p. 99–100°.

Anal. Calcd. for $C_{15}H_{22}N_2O$: N (basic), 5.69. Found: N (basic), 5.66 (titration).

A 36.9 g. sample of the crude tetrahydropyranylpiperazine was suspended in 200 ml. of methanol and hydrogenated with 0.5 g. of Adams catalyst at room temperature under 3.52 kg./cm.^{2} of hydrogen. The calculated amount of hydrogen was taken up in 22 hr. The catalyst was removed and the filtrate was freed from solvent to give a colorless solid. One recrystallization from benzene–Skelly B gave needles of m.p. 77–78°, yield 28.1 g. (75.5%). A sample was recrystallized again to give fine needles of m.p. 78–78.5°, $\nu_{max}^{CHCl_3}$ 3570 cm.$^{-1}$ (free OH).

Anal. Calcd. for $C_{15}H_{28}N_2O$: (basic), N, 5.61. Found: N (basic) 5.62 (titration).

(7) R. K. S. Lim, K. Rink, H. Glass, and E. Soulje-Echagüe, *Arch. Intern. Pharmacodyn.*, **130**, 336 (1960).

(8) R. W. Ryall, *Nature*, **182**, 1606 (1958).

(9) G. C. Stone, B. M. Bernstein, W. E. Hambourger, and V. A. Drill, *Arch. Intern. Pharmacodyn.*, **127**, 85 (1960).

(10) All melting points were corrected. Infrared spectra were measured by Perkin–Elmer Infracord Model 137 spectrophotometer.

The free base was dissolved in 100 ml. of methanol and added to 100 ml. of 2-propanol saturated with dry hydrogen chloride to give the dihydrochloride of m.p. 195–196°, yield 35.1 g., ν_{max}^{KBr} 3420 cm.$^{-1}$ (OH).

Anal. Calcd. for $C_{15}H_{26}Cl_2N_2O$: HCl, 22.7. Found: HCl, 22.6 (titration).

5-(4-Phenyl-1-piperazyl)pentyl 3,4,5-Trimethoxybenzoate Dihydrochloride (XII).—A solution of 1-phenyl-4-(5-hydroxypentyl)piperazine (24.8 g., 0.10 mole) in 100 ml. of chloroform was added to a solution of 3,4,5-trimethoxybenzoyl chloride (23.1 g., 0.10 mole) in 100 ml. of chloroform. The resulting clear solution was refluxed for 3 hr. The crystalline solid which precipitated during this period was collected, washed with ether and dried in air; m.p. 181°, yield 8.8 g. This material was 1-phenyl-4-(5-hydroxypentyl) piperazine monohydrochloride.

Anal. Calcd. for $C_{15}H_{25}ClN_2O$: HCl, 12.8. Found: HCl, 12.8.

The filtrate was evaporated to dryness *in vacuo* to leave a pale yellow syrup which was dissolved in warm methanol, saturated with dry hydrogen chloride and diluted with ethyl acetate to give a colorless solid of m.p. 190–192° dec., yield 18.2 g.; ν_{max}^{KCl} 1710 cm.$^{-1}$ (ester C=O), 1230 cm.$^{-1}$ (ether, $ArOCH_3$).

Anal. Calcd. for $C_{25}H_{36}Cl_2N_2O_5$: HCl, 14.2. Found: HCl, 14.2.

1-Phenyl-4-(4-hydroxybutyl)piperazine.—A solution of 1-phenylpiperazine (178.0 g., 1.1 moles) and 4-chlorobutyl acetate (156.0 g., 1.04 moles) in 300 ml. of 2-propanol in the presence of anhydrous sodium carbonate (160.0 g., 1.5 moles) was stirred under reflux for 20 hr. The inorganic salt was filtered and the filtrate was concentrated *in vacuo* to give a light tan syrup. A solution of this material in 350 ml. of 20% hydrochloric acid was heated under gentle reflux for 3 hr. The solution was clarified with charcoal and made strongly alkaline with aqueous sodium hydroxide to give a tan oil which soon solidified. The product was collected by suction, washed with water and air-dried; yield 157.6 g. (65%), m.p. 67–71°. Recrystallization from aqueous methanol gave the analytical sample, m.p. 65–68°.

Anal. Calcd. for $C_{14}H_{22}N_2O$: N (basic), 5.98. Found: N (basic), 5.88 (titration).

4-(4-Phenyl-1-piperazyl)butyl 3,4,5-trimethoxybenzoate Dihydrochloride (VIII).—To a solution of 1-phenyl-4-(4-hydroxybutyl)piperazine (132 g., 0.565 mole) in 300 ml. of chloroform was added a solution of 3,4,5-trimethoxybenzoyl chloride (130 g., 0.565 mole) in 250 ml. of chloroform all at once. The solution was refluxed for 3 hr. and the solvent was removed *in vacuo* to give a light tan semi-solid. The material was suspended in 500 ml. of methanol and treated with 250 ml. of 2-propanol containing excess hydrogen chloride (27.6 g., 0.76 mole) to give a colorless solid. Another 250 ml. of 2-propanol was added and the suspension was kept at room temperature overnight. The dihydrochloride was collected by suction, washed with ethyl acetate–ether and dried in a vacuum desiccator; yield 242 g. (87%), m.p. 198.5–199.5° dec, ν_{max}^{KBr} 1710 cm.$^{-1}$ (ester C=O), 1230 cm.$^{-1}$ (ether, $ArOCH_3$).

Anal. Calcd. for $C_{24}H_{34}Cl_2N_2O_5$: HCl, 14.6. Found: HCl, 14.6.

1-*p*-Methoxyphenyl-4-(2-hydroxyethyl)piperazine.—A solution of N,N-bis(2-chloroethyl)-*p*-anisidine hydrochloride (68.8 g. 0.232 mole) and ethanolamine (73.0 g., 1.2 moles) in 150 ml. of 2-propanol was heated under reflux for 5 hr. The solvent was removed *in vacuo* and the residue was stirred in water to give 41.2 g. (75.5%) of the product melting at 88–89°. A sample was recrystallized from benzene–Skelly B to give colorless prisms of m.p. 92–93°.

Anal. Calcd. for $C_{13}H_{20}N_2O_2$: N (basic), 5.93. Found: N (basic), 5.86 (titration).

2-(4-*p*-Methoxyphenyl-1-piperazyl)ethyl 3,4,5-trimethoxybenzoate Dihydrochloride (III).—A mixture of the above piperazinylalkanol (23.6 g., 0.10 mole) and 3,4,5-trimethoxybenzoyl chloride (23.1 g., 0.10 mole) in 150 ml. of chloroform was heated under reflux for 1 hr. The solvent was removed *in vacuo* to leave a tan syrupy solid which was treated with methanolic hydrogen chloride. The hot solution was diluted with ethyl acetate to give a colorless powder of m.p. 1[illegible]1° (softening at 190°), yield 42.2 g. (84%). It was once recrystallized from aqueous methanol–ethyl acetate to give crystals of m.p. 205–206° dec, yield 30.0 g.

Anal. Calcd. for $C_{23}H_{32}Cl_2N_2O_6$: HCl, 14.5. Found: HCl, 14.5 (titration).

4-Phenyl-1-[2-(*p*-Methoxyphenylcarbamoyloxy)ethyl]piperazine (XIII).—A mixture of 20.6 g. (0.10 mole) of 1-(2-hydroxyethyl)-4-phenylpiperazine and 14.9 g. (0.10 mole) of *p*-methoxyphenyl isocyanate[11] in 150 ml. of dry benzene was heated under reflux for 6 hr. The benzene solution was cooled and an equal volume of ether was added. The crystalline precipitate was collected, washed with ether and dried to give 26.0 g. (73%) of product, m.p. 120–122°; $\nu_{max}^{CHCl_3}$ 1740 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{25}N_3O_3$: N (basic), 3.94. Found: N, 3.92 (titration).

A solution of the free base in methanol was treated with excess methanolic hydrogen chloride. The *dihydrochloride* was obtained in the form of small white crystals, m.p. 212.5–213° dec.

Anal. Calcd. for $C_{20}H_{27}Cl_2N_3O_3$: Cl, 16.6. Found: Cl, 16.5.

The base was dissolved in benzene and treated with a two-fold excess of methyl iodide. The mixture was heated under reflux for 1 hour; then the benzene was distilled *in vacuo*. The residue was recrystallized from methanol–ether to give the *monomethiodide*, m.p. 145–147°.

Anal. Calcd. for $C_{21}H_{28}IN_3O_3$: N (basic), 2.82. Found: N (basic), 2.82 (titration).

3,4,5-Trimethoxybenzoyl Azide.—To a stirred solution of 57.8 g. (0.25 mole) of 3,4,5-trimethoxybenzoyl chloride in 300 ml. of acetone at 10° was added a solution of 20 g. (0.31 mole) of sodium azide in 100 ml. over a 45-min. period. The mixture was allowed to warm to room temperature, then diluted with 1 l. of water to ensure maximum precipitation of the azide. The white solid was filtered, washed with water and dried to give 58.0 g. (98%) of product, m.p. 85.5–86.5°; $\nu_{max}^{CHCl_3}$ 2150 ($-N_3$), 1700 (CON_3) and 1335 cm.$^{-1}$ ($-N_3$).

4-Phenyl-1-[2-(3,4,5-trimethoxyphenylcarbamoyloxy)ethyl]-piperazine (XVI).—To a solution of 2.37 g. (0.010 mole) of 3,4,5-trimethoxybenzoyl azide in 30 ml. of dry benzene was added 2.06 g. (0.010 mole) of 4-phenyl-1-(2-hydroxyethyl)piperazine. The mixture was heated under reflux for 5 hr. The benzene solution was distilled and ether was added to the residue. The white solid which formed was collected and dried to yield 3.81 g. (92%) of carbamate, m.p. 124–125°. Recrystallization from benzene–ether produced the analytical sample, m.p. 124.5–125.5°; $\nu_{max}^{CHCl_3}$ 1740 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{29}N_3O_5$: N, 10.1. Found: N, 10.0.

A solution of the base in methanol–ether was treated with a two-fold excess of oxalic acid in methanol. The oxalate salt was recrystallized from methanol–ether, m.p. 155–156°.

Anal. Calcd. for $C_{24}H_{31}N_3O_9$: N, 8.32. Found: N, 8.24.

A solution of the base and excess methyl iodide was heated under reflux for 2 hr. After removal of the solvent, the residue was recrystallized from aqueous methanol to give the *monomethiodide*, m.p. 211–212° dec.

Anal. Calcd. for $C_{23}H_{32}IN_3O_5$: N (basic), 2.51. Found: N (basic), 2.52 (titration).

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