weighed 14.7 g. (42.5%) m.p. 250°. An analytical sample was obtained by ethanol crystallization.

Anal. Calcd. for $C_{11}H_{11}ClN_2O_4S$: C, 43.63; H, 3.66; N, 9.26; S, 10.59. Found: C, 43.16; H, 3.75; N, 9.03; S, 11.15.

N-(7-Chloro-4-quinolyl)ethyleneimine. A slurry of 14.7 g. of quinolylaminoethylsulfuric acid in 25 ml. of water was stirred during the addition of 50 ml. of 40% sodium hydroxide. The mixture was heated with stirring in an open beaker; when the temperature reached about 140°, a visible reaction occurred, after which a sample showed solubility in dilute acetic acid. Following separation and washing by decantation, the oily product solidified. After leaching with dilute acetic acid, filtering and precipitating, the product again became oily and was separated by decantation, leached several times with warm benzene, and carboned in the organic layer. Concentration and addition of hexane, yielded 3.8 g. (38%) of crude crystalline product, m.p. 87–91°. After several precipitations from dilute acetic acid–ethanol mixtures and one crystallization from hexane, 1.05 g., m.p. 95–96° remained. A previously obtained vacuum sublimed analytical sample melted at 94.0–95.5°.

Anal. Calcd. for $C_{11}H_9ClN_2$: C, 64.55; H, 4.43; N, 13.69; Cl, 17.33. Found: C, 64.76; H, 4.30; N, 13.08; Cl, 17.26.

2-(6-Chloro-2-methoxy-9-acridinyl)ethylsulfuric acid. This compound was prepared from 6-chloro-2-methoxy-9-(2-hydroxyethylamino)acridine[13] and concentrated sulfuric acid at room temperature in essentially the same manner as the 7-chloro-4-quinolyl compound above. The yield after reprecipitation from dilute sodium hydroxide and alcohol with acetic acid was 93%, m.p. 300–305° dec.

Anal. Calcd. for $C_{16}H_{15}ClN_2O_5S\frac{1}{2}H_2O$: C, 49.04; H, 4.12; N, 7.15; S, 8.19. Found: C, 49.13; H, 4.09; N, 7.05; S, 8.20.

N-(6-Chloro-2-methoxy-9-acridinyl)ethylenimine. A mixture of 5.5 g. of the sulfuric acid ester and 25 ml. of 50% sodium hydroxide was stirred and heated in a beaker at 150° for about 1 hr., cooled, diluted, filtered and washed. The crude material was taken up in about 20 ml. of glacial acetic acid, diluted, and filtered (about 1.5 g. was insoluble). The soluble material was precipitated with alkali; it weighed 3.2 g. The precipitation from dilute acetic acid was repeated in the presence of an equal volume of alcohol, giving 0.6 g. (15%), m.p. 185–188°. Two sublimations at 180°/0.1 μ gave 0.4 g. (10%) of product, m.p. 184–187°.

Anal. Calcd. for $C_{16}H_{13}ClN_2O$: C, 67.49; H, 4.60; N, 9.84. Found: C, 67.28, 67.00; H, 4.73, 4.59; N, 9.79, 9.65.

7-Chloro-4-[2-bis(2-chloroethyl)-N-oxyaminoethylamino]-quinoline dihydrochloride. A solution of 20 g. of 7-chloro-4-{[2-bis(2-chloroethyl)aminoethylamino]} quinoline dihydrochloride monohydrate[2] in 400 ml. of glacial acetic acid was cooled to room temperature and 26 ml. of 40% peracetic acid was added. The temperature rose slowly to 35°, was kept there for an hour and then brought to 45° for 15 min. and momentarily to 60°. After cooling, 2 ml. of hydrochloric acid and 250 ml. of acetone were added, the mixture was diluted to 1 l. with dry ether and cooled for 1 week. The crystalline precipitate was filtered and washed; it weighed 16.3 g. This was dissolved in water; acetone and ether were added to give two crops of product. The first contained more than two molecules of hydrogen chloride; the second weighed 5.1 g. (26% of the theoretical). See Table I.

Part D. Aliphatic 2-chloroethyl compounds (Mustards derived from side chains). These compounds were prepared by the addition of the hydroxyethyl precursor, as its dihydrochloride, to an excess of stirred thionyl chloride. The mixture was warmed to complete the reaction, excess thionyl chloride was removed under water pump vacuum, and the residue was recrystallized twice from absolute ethanol containing a trace of concentrated hydrochloric acid. The products were obtained as hygroscopic, sharp-melting crystalline dihydrochlorides (See Table II).

PHILADELPHIA 11, PA.

(13) J. H. Burckhalter *et al.*, *J. Am. Chem. Soc.*, **65**, 2012 (1943).

[CONTRIBUTION FROM THE CHEMICAL THERAPEUTICS RESEARCH LABORATORY, MILES LABORATORIES, INC.]

New Sedative and Hypotensive Phenylpiperazine Amides

SHIN HAYAO AND R. N. SCHUT

Received February 9, 1961

A number of *N*-(4-aryl-1-piperazyl)alkylpolymethoxybenzamides and *N*-polymethoxyphenyl(4-aryl-1-piperazyl)alkanoic acid amides and the corresponding hydrochlorides were prepared. Infrared spectra of stable amidonium chlorides are discussed. A transamidation reaction took place during the synthesis of butyramide derivatives and this may involve a cyclic intermediate.

The presence of the 3,4,5-trimethoxybenzoyl group in reserpine led to a search for pharmacologically active trimethoxybenzamide derivatives.[1] Weinberg *et al.*[2] reported that trimethoxybenzoic acid esters of amino alcohols lacking the indole ring system showed sedative properties of the reserpine type. Bovet[3] found that 1-phenylpiperazine and 1-methyl-4-phenylpiperazine reverse the pressor response to adrenaline. Also 1-phenyl-4-homoveratrylpiperazine[4] is reported to be similar to chlorpromazine in its central depressant properties.

These findings suggested the synthesis of new sedative and hypotensive agents which contain both 1-phenylpiperazine and 3,4,5-trimethoxybenzoyl groups. We prepared a series of *N*-(4-aryl-1-piperazyl)alkylpolymethoxybenzamides (Class A) and another series of *N*-polymethoxyphenyl(4-aryl-1-piperazyl)alkanoic acid amides (Class B) as follows:

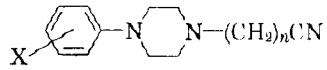
(1) (a) Y. G. Perron, U. S. Pat. **2,870,145**; **2,870,156** (1959). (b) G. P. Schiemenz and H. Engelhart, *Ber.*, **92**, 857, 862 (1959).

(2) M. S. Weinberg *et al.*, Abstr. from 130th Am. Chem. Soc. Meeting, Atlantic City, 1956, 11N.

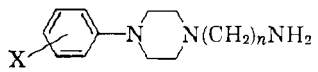
(3) D. Bovet and F. Bovet-Nitti, *Médicaments du Système Nérveux Vegetatif*, S. Karger, S. A. Bale, 1948, p. 247.

(4) J. Mills, M. M. Boren, and N. R. Easton, Abstr. from 132nd Am. Chem. Soc. Meeting, New York, 1957 11-O.

TABLE I

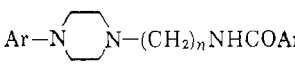
A. 

X	n	Formula	M.P.	Yield, %	Nitrogen, %[a] Calcd.	Found
H	1	$C_{12}H_{15}N_3$	79–81[d]	63.0	6.97	6.89
p-CH_3	1	$C_{13}H_{17}N_3$	122–122.5	67.0	6.51	6.66
p-Cl	1	$C_{12}H_{14}ClN_3$	120–122	85.0	5.94	6.08
H	2	$C_{13}H_{17}N_3$	75[e]	94.5	19.5	19.7[b]
p-CH_3	2	$C_{14}H_{19}N_3$	70–72[f]	82.8	6.11	6.07
p-CH_3O	2	$C_{14}H_{19}N_3O$	80–81.5	92.5	5.71	5.48
p-Cl	2	$C_{13}H_{16}ClN_3$	107–109	53.0	5.61	5.42
o-Cl	2	$C_{13}H_{16}ClN_3$	176–174 (0.15 mm.)[e]	82.8	5.61	5.69
H	3	$C_{14}H_{19}N_3$	171–172 (0.4 mm.)[e]	89.5	6.11	6.07
p-Cl	3	$C_{14}H_{18}ClN_3$	66–68	92.0	—	—
H	4	$C_{15}H_{21}N_3$	172–175 (0.1 mm.)[e]	64.0	5.76	5.76
H	5	$C_{16}H_{23}N_3$	69–70	86.4	5.45	5.51
H	6	$C_{17}H_{25}N_3$	186–194 (0.18–0.45)	58.0	5.17	5.18

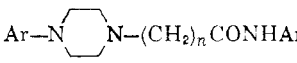
B. 

X	n	Formula	M.P.	Yield, %	Nitrogen, %[a] Calcd.	Found
H	2	$C_{12}H_{19}N_3$	122–132 (0.08–0.35)[g]	79.5	13.7	13.2
p-Cl	2	$C_{12}H_{18}ClN_3$	152–166 (0.35–0.40)	81.0	11.7	11.6
p-CH_3	2	$C_{13}H_{21}N_3$	126–135.5 (0.25–0.40)[h]	84.5	12.8	12.9
H	3	$C_{13}H_{21}N_3$	139–140 (0.4)[i]	91.0	12.9	12.5
p-CH_3	3	$C_{14}H_{23}N_3$	162–158 (1.4–0.9)	90.0	12.0	11.8
p-CH_3O	3	$C_{14}H_{23}N_3O$	166–169 (0.15–0.2)	91.5	11.3	11.0
p-Cl	3	$C_{13}H_{20}ClN_3$	160–166 (0.15–0.17)	80.0	11.1	10.7
o-Cl	3	$C_{13}H_{20}ClN_3$	148–156 (0.3–0.45)	84.0	11.1	11.1
H	4	$C_{14}H_{23}N_3$	146–147 (0.3)	73.5	12.0	11.7
p-Cl	4	$C_{14}H_{22}ClN_3$	167–170 (0.15–0.3)	71.5	10.5	10.9
H	5	$C_{15}H_{25}N_3$	181–183 (1.0–1.75)	72.0	11.3	11.4
H	6	$C_{16}H_{27}N_3$	178–184 (0.4–0.5)	91.0	10.7	10.6
H	7	$C_{17}H_{29}N_3$	171–180 (0.16–0.35)	82.5	10.18	9.84

[a] Basic nitrogen by titration with perchloric acid. [b] Total nitrogen. [c] Boiling point. [d] Lit. m.p. 75–76°, C. B. Pollard and L. J. Hughes, *J. Am. Chem. Soc.*, **77**, 40 (1955). [e] Lit. m.p. 71.3–72.1°, C. B. Pollard, *et al.*, *J. Am. Chem. Soc.*, **75**, 2989 (1953). [f] Lit. m.p. 70.4–71.4°, *ibid.* [g] Lit. b.p. 175–180° (0.5 mm.), E. Cerkovnikov and P. Stern, *Arkiv. Kem.*, **18**, 12 (1946). [h] M.p. 64–66°. [i] Lit. b.p. 178–183° (6 mm.), K. Fujii, *J. Pharm. Soc. Japan*, **76**, 637 (1956).



Class A:
wherein
Ar = C_6H_5, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, 4-ClC_6H_4, 2-ClC_6H_4
Ar′ = C_6H_5, 4-$CH_3OC_6H_4$, 3,4-$(CH_3O)_2C_6H_3$, 3,4,5-$(CH_3O)_3C_6H_2$, 3-$(CH_3)_2NC_6H_4$
n = 2, 3, 4, 5, 6, 7



Class B:
wherein
Ar = C_6H_5, 4-$CH_3C_6H_4$, 4-ClC_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-$(CH_2O_2)C_6H_3CH_2$, 3,4-$(CH_3O)_2C_6H_3CH_2CH(CH_3)$
n = 1,2,3,4

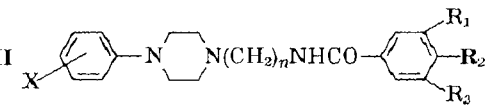
The compounds in Class A were prepared as follows: The appropriate nitriles were obtained from 1-phenylpiperazine with acrylonitrile or an ω-haloalkyl cyanide. These nitriles were readily hydrogenated in methanolic ammonia using Raney nickel catalyst to form the corresponding amines in high yield. The amines reacted with substituted benzoyl chlorides by the Schotten-Baumann method to give the desired amides. The nitriles and the amines are shown in Table I. The amides and their hydrochlorides are listed in Table II.

The compounds in Class A generally gave stable dihydrochlorides in methanolic hydrogen chloride. However, compounds VIII, IX, and XIII gave *dihydrochloride monomethanolates*. On the other hand, compounds V, VI, VII, and XIX gave stable *trihydrochlorides*. The absence of N—H stretching (*ca.* 3300 cm.$^{-1}$) and the amide II band (*ca.* 1550 cm.$^{-1}$, due to N—H bending plus C=O and C—N in-phase stretching)[5] in the infrared spectra indicated the formation of amidonium ions. The amide I bands (*ca.* 1640 cm.$^{-1}$ due to C=O and C—N out-of-phase stretching) were practically unaffected.

The formation of hydrochlorides of some ali-

(5) T. Miyazawa, T. Shimanouchi, and S. Mizushima, *J. Chem. Phys.*, **24**, 408 (1956); L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd ed., Wiley, New York, 1958, pp. 205, 220

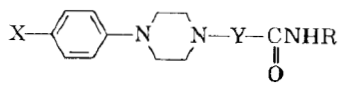
TABLE II



No.	X	n	R_1	R_2	R_3	Formula	M.P.	Yield, %	Nitrogen, % Calcd.	Nitrogen, % Found	Hydrogen Chloride, % Calcd.	Hydrogen Chloride, % Found
I	H	2	OCH_3	OCH_3	OCH_3	$C_{22}H_{29}N_3O_4$	176–177	97	10.5	10.9		
						·2HCl	215–216				15.5	15.2
II	*p*-CH_3	2	H	OCH_3	H	$C_{21}H_{27}N_3O_2$	189–190	96.8	11.9	11.8		
						·2HCl	228–230 dec.				17.1	17.1
III	*p*-CH_3	2	OCH_3	OCH_3	OCH_3	$C_{23}H_{31}N_3O_4$	187–188	100	10.2	10.3		
						·2HCl	232–232.5 dec.				15.0	14.9
IV	*p*-Cl	2	OCH_3	OCH_3	OCH_3	$C_{22}H_{27}ClN_2O_5$	164–165	100	9.69	9.83		
						·2HCl	194–194.5 dec.				14.4	14.1
V	H	3	H	H	H	$C_{20}H_{25}N_3O$	112–113[c]	95.5	13.0	13.1		
						·3HCl	209–210		4.33	4.44[a]	25.3	25.1
VI	H	3	H	OCH_3	H	$C_{21}H_{27}N_3O_2$	128–130	99.0	11.9	12.2		
						·3HCl	198–198.5 dec.				23.7	23.4
VII	H	3	OCH_3	OCH_3	H	$C_{22}H_{29}N_3O_3$	132–134	58.0	11.0	11.1		
						·3HCl	204–205 dec.[b]		8.53	8.65	22.2	21.7, 21.9
VIII	H	3	OCH_3	OCH_3	OCH_3	$C_{23}H_{31}N_3O_4$	145–146.5	86.8	10.2	10.4		
						·2HCl·CH_3OH	177–178 dec.		8.11	8.06	14.1	13.9
IX	H	3	H	H	$N(CH_3)_2$	$C_{22}H_{30}N_4O$	124–124.5	63.2	7.65	7.43[a]		
						·3HCl·CH_3OH	171–172 dec.				21.6	21.3
X	*p*-CH_3	3	H	H	$N(CH_3)_2$	$C_{23}H_{32}N_4O$	110.5–111	88.0	7.37	7.28[a]		
						·3HCl	161–163 dec.				22.4	22.4
XI	*p*-CH_3	3	OCH_3	OCH_3	OCH_3	$C_{24}H_{33}N_3O_4$	119–120	87.0	9.83	9.85		
						·2HCl·CH_3OH	205 dec.		7.89	7.85	13.7	13.5
XII	*p*-CH_3O	3	OCH_3	OCH_3	OCH_3	$C_{24}H_{33}N_3O_5$	128–129	92.8	9.48	9.69		
						·2HCl	202–204 dec.				14.2	14.0
XIII	*p*-Cl	3	OCH_3	OCH_3	OCH_3	$C_{23}H_{30}ClN_3O_4$	134–136	100	9.02	8.95		
						·2HCl·CH_3OH	178–180 dec.		7.60	7.55	13.2	12.9
XIV	*o*-Cl	3	OCH_3	OCH_3	OCH_3	$C_{23}H_{30}ClN_3O_4$	150.5–151	72.5	9.39	9.50		
						·HCl	192.5–193.5				7.54	7.60
XV	H	4	OCH_3	OCH_3	OCH_3	$C_{24}H_{33}N_3O_4$	153–154	99.0	9.83	9.71		
						·2HCl	243–244 dec.				14.6	14.3
XVI	*p*-Cl	4	OCH_3	OCH_3	OCH_3	$C_{24}H_{32}ClN_3O_4$	147–148	74.2	9.10	9.27		
						·2HCl	176–176.5 dec.				13.7	13.7
XVII	H	5	OCH_3	OCH_3	OCH_3	$C_{25}H_{35}N_3O_4$	100–102	94.5	9.52	9.68		
						·2HCl	166–168 dec.				14.2	14.3
XVIII	H	5	H	OCH_3	H	$C_{23}H_{31}N_3O_2$	123–124	97.5	11.02	11.20		
						·2HCl	221–222 dec.				16.1	15.9
XIX	H	6	OCH_3	OCH_3	OCH_3	$C_{26}H_{37}N_3O_4$	145–146	99.5	9.23	9.34		
						·3HCl	174–175 dec.				19.4	19.0
XX	H	7	OCH_3	OCH_3	OCH_3	$C_{27}H_{39}N_3O_4$	95–96	93.5	8.95	9.07		
						·2HCl	189–190				13.5	13.5
XXI	H	7	H	OCH_3	H	$C_{25}H_{35}N_3O_2$	123.5–124.5	84.0	3.42	3.48[a]		
						·$C_4H_4O_4$[d]	107.5–108.5		8.00	8.10		

[a] Basic nitrogen by titration with perchloric acid. [b] *Anal.* Calcd.: Cl, 21.6. Found: Cl, 21.2 (Parr fusion). [c] Lit. m.p. 109–110°, R. W. Fleming and R. F. Parcell, U. S. Pat. 2,722,529 (1955). [d] Maleate.

TABLE III

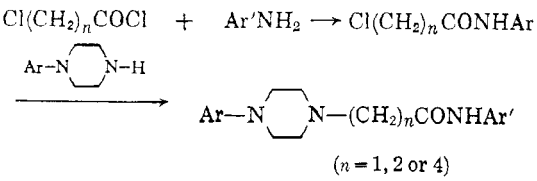


Compd. No.	X	Y	R	Formula	M.P.	Yield, %	Chlorine, % Calcd.	Chlorine, % Found
XXII	H	CH_2	3,4,5-Trimethoxyphenyl	$C_{21}H_{27}N_3O_4$ ·HCl	175.5–176 245–247 dec.	96	8.41	8.36
XXIII	H	$(CH_2)_2$	4-Methoxyphenyl	$C_{20}H_{25}N_3O_2$ ·HCl	172–173 261–262 dec.	88	12.39 9.44	12.57[a] 9.43
XXIV	H	$(CH_2)_2$	3,4-Dimethoxyphenyl	$C_{21}H_{27}N_3O_3$ ·HCl	138–140 272–273	65	8.74	8.59
XXV	H	$(CH_2)_2$	3,4-Methylenedioxyphenyl	$C_{20}H_{23}N_3O_3$ ·HCl	141–142 248–249 dec.	61	9.10	9.09
XXVI	H	$(CH_2)_2$	3,4,5-Trimethoxyphenyl	$C_{22}H_{29}N_3O_4$ ·HCl	143–145 223–224	89	8.14	8.29
XXVII	H	$(CH_2)_2$	3,4-Methylenedioxybenzyl	$C_{21}H_{25}N_3O_3$ ·HCl	122–124 233–234 dec.	56	8.79	8.79
XXVIII	H	$(CH_2)_2$	3,4,5-Trimethoxybenzyl	$C_{23}H_{31}N_3O_4$ ·2HCl	115–117 173–174 dec.	71	14.58	14.29
XXIX	H	$(CH_2)_2$	α-Methylhomoveratryl	$C_{24}H_{33}N_3O_3$ ·HCl	112–113 220–221 dec.	73	7.92	7.88
XXX	H	$CHCH_3$	3,4-Dimethoxyphenyl	$C_{21}H_{27}N_3O_3$ ·2HCl	212.5–214 dec.	57[b]	16.07	15.88
XXXI	H	$CHCH_3$	3,4,5-Trimethoxyphenyl	$C_{22}H_{29}N_3O_4$ ·2HCl	219–220 dec.	23[b]	15.01	15.06
XXXII	Cl	$(CH_2)_2$	3,4,5-Trimethoxyphenyl	$C_{22}H_{28}ClN_3O_4$ ·2HCl	155–156 223.4–224.5 dec.	78	7.55	7.46
XXXIII	CH_3	$(CH_2)_2$	3,4,5-Trimethoxyphenyl	$C_{23}H_{31}N_3O_4$ ·HCl	137.5–138.5 239–240 dec.	64	7.89	7.93
XXIV	H	$(CH_2)_3$	3,4,5-Trimethoxyphenyl	$C_{23}H_{31}N_3O_3$ ·2HCl	159–160 220–221 dec.	6.3	10.17 14.58	10.24[a] 14.42
XXXV	H	$(CH_2)_4$	3,4,5-Trimethoxyphenyl	$C_{24}H_{33}N_3O_3 \cdot H_2O$ ·2HCl	156–157 262–264	68.0	9.44 14.20	9.35[a] 13.95

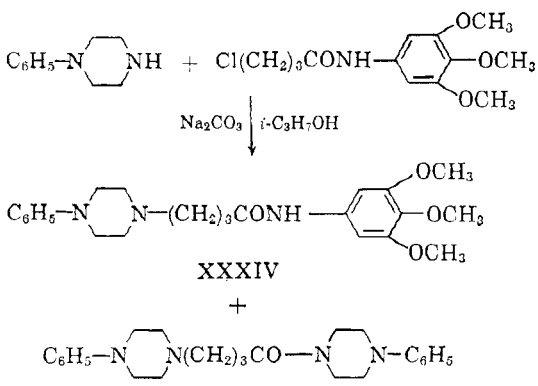
[a] Nitrogen by Kjeldahl. [b] Yield of dihydrochloride.

phatic acid amides[6] has been reported. The absence of N—H stretching absorption in the infrared spectrum of *N*-ethylacetamide in carbon tetrachloride containing an equivalent amount of hydrogen chloride led Canon[7] to suggest the presence of a protonated amide, but he mentioned nothing concerning the carbonyl region.

The compounds in Class B (Table III) were prepared as follows:

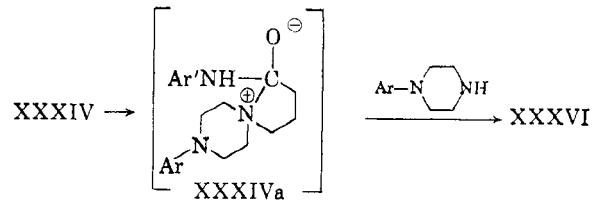


These compounds were obtained in fair to good yields in all cases except when $n = 3$.



The reaction of *N*-phenylpiperazine with *N*-(3,4,5-trimethoxyphenyl)-4-chlorobutyramide (mole ratio 1:1) gave 4-phenyl-1-[4-(4-phenyl-1-piperazyl)]-butyrylpiperazine (XXXVI) in 62% yield. Only a small amount (6.3%) of the desired product (XXXIV) was isolated. In contrast, when *N*-(3,4,5-trimethoxyphenyl)-5-chlorovaleramide was used, compound XXXV was obtained in 65% yield.

The predominance of transamidation reaction when $n = 3$ might be explained in the following way. The piperazine nitrogen in the initial product XXXIV may participate in formation of the cyclic intermediate XXXIVa. Another mole of *N*-phenylpiperazine may then displace the weaker aromatic amine by an S_N2 mechanism to give compound XXXVI. In the case where $n = 4$, the distance factor[8] becomes more important and formation of the cyclic intermediate would occur at a considerably slower rate. Examples of this type of intramolecular catalysis in hydrolysis reactions have been reported by Bender[9] and Bruice.[10]



Pharmacology. The acute pharmacological profiles of VIII and reserpine in sedation, motor-relaxation, hypnotic facilitation and convulsive facilitation tests showed that the ED50's are approximately equal; however, VIII is about three times as toxic as reserpine. In contrast to reserpine VIII is only moderately cumulative. It is currently undergoing preliminary clinical trial as a sedative.

The acute toxicity of XXVI is of the same order as that of reserpine. It has strong antihypertensive activity, the ED50 being 6 mg./kg. in dogs by the intravenous route. The compound is also orally active in the unanesthetized normotensive dog. Its sedative activity is similar to that of VIII.

The antihypertensive ED50's of VI are 2.2 mg./kg. (dog intravenous route) and 11 mg./kg. (unanesthetized dog, orally). Its sedative activity is poor. Most of the compounds of both classes are antiadrenergic agents. The details of the pharmacology will be published elsewhere.

EXPERIMENTAL[11]

1-Arylpiperazines. 1-Phenyl-, 1-*p*-tolyl-, *p*-chlorophenyl- and *o*-chlorophenylpiperazines were prepared according to Pollard's procedure.[12] 4-Methoxyphenylpiperazine was prepared by condensation of *N,N*-bis(2-chloroethyl)-*p*-anisidine hydrochloride with benzylamine, followed by catalytic debenzylation.

1-Phenyl-4-[3-(3,4,5-trimethoxybenzamido)propyl]piperazine (VIII). To an ice-cold mixture of 1-phenyl-4-(3-aminopropyl)piperazine (175 g., 0.8 mole) in 150 ml. of benzene and 250 ml. of 20% sodium hydroxide solution was added with stirring a solution of 3,4,5-trimethoxybenzoyl chloride (184 g., 0.8 mole) in 300 ml. of benzene during 45 min. A milky suspension formed and the desired product soon separated as a colorless solid. After stirring for 18 hr. at room temperature, the solid was collected, washed with water and dried in an oven at 50°; yield 286 g. (86.8%), m.p. 142–144.5°. It was recrystallized from 1250 ml. of 80% methanol to give 264 g. of purified product melting at 145–146.5°.

Anal. Calcd. for $C_{23}H_{31}N_3O_3$: N, 10.2. Found: N, 10.4.

The above basic amide was dissolved in 700 ml. of methanol and treated with 450 ml. of methanol containing 83.7 g. (2.3 moles) of hydrogen chloride. Ethyl acetate (250 ml.) was added to the hot solution to precipitate shiny crystals of m.p. 177–178° dec.; yield 328 g. (99.0%).

Anal. Calcd. for $C_{23}H_{33}Cl_2N_3O_4 \cdot CH_3OH$: N, 8.11; HCl, 14.1. Found: N, 8.06; HCl, 13.9.

1-Phenyl-4-(5-cyanopentyl)piperazine. A mixture of 1-phenylpiperazine (244 g., 1.5 mole) and ω-bromocapronitrile[13]

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(11) All melting points are corrected. Infrared spectra were measured by Beckman IR-4 and Perkin-Elmer Spectracord Model 137 spectrophotometers.

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(262 g., 1.49 moles) in 650 ml. of isopropyl alcohol in the presence of anhydrous sodium carbonate (159 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 tan-colored solid. It was recrystallized from aqueous methanol to give 333 g. (86.4%) of product. The analytical sample (from aqueous acetone) melted at 69–70°.

Anal. Calcd. for $C_{16}H_{27}N_3$: N (basic), 10.7. Found: N (basic), 10.6 (titration).

N(p-Methoxyphenyl)-3-(4-phenyl-1-piperazyl)propionamide. The procedure of Pollard, Lauter, and Nuessle[14] was used. To a hot solution of 35.6 g. (0.22 mole) of *N*-phenylpiperazine and 42.8 g. (0.20 mole) of *N*-(*p*-methoxyphenyl)-3-chloropropionamide[15] in 300 ml. of isopropyl alcohol was added 50 g. (0.47 mole) of anhydrous sodium carbonate. The mixture was stirred and heated under reflux for 12 hr. The mixture was cooled and treated with 500 ml. of water. The solid material was collected, washed with water and dried to give 60.0 g. (88%) of *N*-(*p*-methoxyphenyl)-3-(4-phenyl-1-piperazyl)propionamide, m.p. 172–173°. For analysis a sample was recrystallized from aqueous methanol in the form of white powder, m.p. 173–174°.

Anal. Calcd. for $C_{20}H_{25}N_3O_2$: N, 12.4. Found: N, 12.6.

Excess hydrogen chloride was added to a suspension of the piperazylamide in methanol. The mixture was heated on the steam bath for 15 min., cooled and filtered to give the hydrochloride, m.p. 261–262° dec.

Anal. Calcd. for $C_{20}H_{26}ClN_3O_2$: Cl, 9.44. Found: Cl, 9.43.

Other piperazylamides (except XXXIV and XXXV) were synthesized according to the foregoing procedure. The hydrochlorides were prepared and recrystallized from aqueous isopropyl alcohol.

N-(3,4,5-Trimethoxyphenyl)-4-chlorobutyramide. To a stirred solution of 38.6 g. (0.21 mole) of 3,4,5-trimethoxyaniline[16] in 300 ml. of warm benzene and 20 ml. of dry pyridine was added a solution of 32.5 g. (0.23 mole) of 4-chlorobutyryl chloride[17] in 50 ml. of benzene over a 30-min. period. The mixture was stirred until the temperature dropped to 25°. Water (250 ml.) was added and the benzene layer was separated. The extract was washed with 5% hydrochloric acid and water, then concentrated *in vacuo* to yield a brown syrup which crystallized upon the addition of ether. The crude material was recrystallized from methanol-ether to give 45 g. (75%) of product, m.p. 118–119°; $\nu_{max}^{CHCl_3}$ 1685 (amide C=O) and 3500 cm.$^{-1}$ (N—H). The analytical sample was produced by one more recrystallization from methanol-ether, m.p. 118–119°.

Anal. Calcd. for $C_{13}H_{18}ClNO_4$: Cl, 12.3. Found: Cl, 12.2 (Parr fusion).

4-Phenyl-1-[4-(4-phenyl-1-piperazyl)]butyrylpiperazine (XXXVI). A mixture of 57.0 g. (0.197 mole) of *N*-(3,4,5-trimethoxyphenyl)-4-chlorobutyramide, 29.0 g. (0.179 mole) of *N*-phenylpiperazine, 50 g. of anhydrous sodium carbonate, and 2 g. of sodium iodide in 500 ml. of isopropyl alcohol was stirred under reflux for 2 days. The mixture was filtered while hot and the filtrate was concentrated *in vacuo*. The residue was dissolved in isopropyl alcohol–ethyl acetate and treated with excess hydrogen chloride. A solution of the crude hydrochloride in 250 ml. of water was shaken with benzene to remove starting amide. Treatment of the aqueous phase with sodium carbonate solution gave 54 g. of a tan solid. It was recrystallized from aqueous methanol to give 13 g. of colorless crystalline product of m.p. 115–117°. From the filtrate was isolated an additional 9.0 g. of product melting at 115–117°, making a total yield of 22.0 g. (62%). A sample was recrystallized from aqueous methanol, m.p. 116.5–117.5°, $\nu_{max}^{CHCl_3}$ 1640 cm.$^{-1}$ (amide C=O).

Anal. Calcd. for $C_{24}H_{32}N_4O$: N, 14.3. Found: N, 14.2.

Addition of excess hydrogen chloride to an ethyl acetate–isopropyl alcohol solution of the free base resulted in the formation of a trihydrochloride (shown by titration curve). Recrystallization from isopropyl alcohol containing a minimal amount of water gave the dihydrochloride, m.p. 216–218° dec.

Anal. Calcd. for $C_{24}H_{34}Cl_2N_4O$: Cl, 15.3. Found: Cl, 15.0.

N-(3,4,5-Trimethoxyphenyl)-4-(4-phenyl-1-piperazyl)-butyramide (XXXIV). Concentration of the filtrate from the aforementioned free base produced 4.8 g. (6.3%) of the desired amide, m.p. 152–154°. Recrystallization from aqueous methanol gave the analytical sample, m.p. 159–160°; $\nu_{max}^{CHCl_3}$ 1680 cm.$^{-1}$ (amide C=O).

Anal. Calcd. for $C_{23}H_{31}N_3O_4$: N, 10.2. Found: N, 10.2.

Addition of excess hydrogen chloride to a solution of the free base in isopropyl alcohol gave the dihydrochloride, m.p. 218.5–219.5° dec.

Anal. Calcd. for $C_{23}H_{33}Cl_2N_3O_4$: Cl, 14.6. Found: Cl, 14.5.

N-(3,4,5-Trimethoxyphenyl)-5-(4-phenyl-1-piperazyl)-valeramide hydrate (XXXV). A mixture of 36.1 g. (0.12 mole) of *N*-(3,4,5-trimethoxyphenyl)-5-chlorovaleramide and 38.9 g. (0.24 mole) of *N*-phenylpiperazine in 250 ml. of *t*-butyl alcohol was heated under reflux for 2 hr. The alcohol was distilled *in vacuo* and the residue was shaken with a chloroform-water mixture. The chloroform extract was dried and concentrated *in vacuo* to give 58 g. of oil which solidified when triturated with ether. The crude material was recrystallized twice from aqueous methanol to give 34.5 g. (65%) of product, m.p. 156–157°; $\nu_{max}^{CHCl_3}$ 1680 cm.$^{-1}$ (amide C=O).

Anal. Calcd. for $C_{24}H_{33}N_3O_4 \cdot H_2O$: N, 9.44. Found: N, 9.35.

Addition of excess hydrogen chloride to a solution of the free base in isopropyl alcohol–ethyl acetate produced the dihydrochloride, m.p. 262–264° (dec.).

Anal. Calcd. for $C_{24}H_{35}Cl_2N_3O_4$: Cl, 14.2. Found: Cl, 14.0.

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