



TABLE I

No.	R	Method <sup>a</sup>	Yield, <sup>b</sup> %	Bp (mm) or mp, °C	<i>n</i> <sub>D</sub> (°C) or recrystn solvent	Formula	Analyses	Antiviral act. <sup>c</sup>	
1	CH <sub>3</sub> <sup>d</sup>	B	80	118-120 (0.5)	1.4715 (25)	C <sub>12</sub> H <sub>25</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	++	
2	H <sup>d</sup>	B	36 <sup>e</sup>	118-121 (0.5)	1.4805 (25)	C <sub>11</sub> H <sub>23</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	-	
3	CH <sub>3</sub> CH <sub>2</sub>	A	68	106 (0.2)	1.4736 (25)	C <sub>13</sub> H <sub>27</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	++	
4	(CH <sub>3</sub> ) <sub>2</sub> CH	A	26	120 (0.2)	1.4723 (26)	C <sub>14</sub> H <sub>29</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	++	
5	CH <sub>2</sub> =CHCH <sub>2</sub>	A	44	108-110 (0.2)	1.4798 (24)	C <sub>14</sub> H <sub>27</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	+	
6	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub>	A	44	128 (0.2)	1.4690 (28)	C <sub>15</sub> H <sub>31</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	-	
7	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub>	A	48	154-160 (1.0)	1.4710 (23)	C <sub>17</sub> H <sub>35</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	-	
8	(CH <sub>3</sub> ) <sub>2</sub> N(CH <sub>2</sub> ) <sub>3</sub>	B	68	163 (0.05)	1.4760 (26)	C <sub>16</sub> H <sub>34</sub> N <sub>4</sub> O <sub>2</sub>	C, H; N <sup>g</sup>	-	
9	CF <sub>3</sub> CH <sub>2</sub> <sup>f</sup>	B	78	97-102 (0.1)	1.4420 (26)	C <sub>13</sub> H <sub>24</sub> F <sub>3</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	-	
10	C <sub>6</sub> H <sub>5</sub> <sup>d</sup>	B	49	175-178 (1.0)	1.5328 (25)	C <sub>17</sub> H <sub>27</sub> N <sub>3</sub> O <sub>2</sub>	C, N; H <sup>h</sup>	-	
11	2HCl·C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> <sup>d</sup>	A	66	194-196	EtOH-Et <sub>2</sub> O	C <sub>18</sub> H <sub>31</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>2</sub> ·0.5H <sub>2</sub> O	C, H, N	-	
12	CH <sub>3</sub> COCH <sub>2</sub>   CH <sub>3</sub>	A	30	157 (0.15)	1.4799 (22)	C <sub>14</sub> H <sub>27</sub> N <sub>3</sub> O <sub>3</sub>	C, H, N	-	
13	H <sub>2</sub> NCSNHN=C(CH <sub>3</sub> ) <sub>2</sub>		20	137-139	EtOH-Et <sub>2</sub> O	C <sub>15</sub> H <sub>30</sub> N <sub>5</sub> O <sub>2</sub> S	C, H, N		
14	2HCl·		26	120-125	EtOH or MeCN	C <sub>16</sub> H <sub>28</sub> Cl <sub>2</sub> N <sub>4</sub> O <sub>4</sub>	C, H, N	-	
15	OCH		52	158 (0.1)	1.4934 (24)	C <sub>12</sub> H <sub>23</sub> N <sub>3</sub> O <sub>3</sub>	C, H; N <sup>i</sup>	-	
16	ON		83	149-152 (0.25)	1.4972 (25)	C <sub>11</sub> H <sub>22</sub> N <sub>4</sub> O <sub>3</sub>	C, H; N <sup>j</sup>	-	
17	H <sub>2</sub> N		40	124-130 (0.2)	1.4898 (22)	C <sub>11</sub> H <sub>24</sub> N <sub>4</sub> O <sub>2</sub>	C, H; N <sup>k</sup>	-	
18	H <sub>2</sub> NCO		59	85-86	CHCl <sub>3</sub> -EtO <sub>2</sub>	C <sub>12</sub> H <sub>24</sub> N <sub>4</sub> O <sub>3</sub>	C, H; H <sup>l</sup>	-	

<sup>a</sup> General methods are described in the Experimental Section. If there is no notation in the method column the experiment is described individually in the Experimental Section. <sup>b</sup> In many examples the stated yield is the result of only one experiment and does not indicate a maximum yield. <sup>c</sup> ++ = 60-80% survival, + = 35-60% survival, and - = rejected as inactive. <sup>d</sup> First described in ref 3a. <sup>e</sup> See footnote 8. <sup>f</sup> The starting material for **9** was prepared as in ref 20. <sup>g</sup> N: calcd, 17.8; found, 17.1. <sup>h</sup> H: calcd, 8.9; found, 8.4. <sup>i</sup> N: calcd, 16.3; found, 15.8. <sup>j</sup> N: calcd, 21.7; found, 21.2. <sup>k</sup> N: calcd, 22.9; found, 22.4. <sup>l</sup> H: calcd, 8.8; found, 8.0.

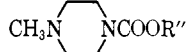
TABLE II











No.	R'	Method <sup>a</sup>	Yield, <sup>b</sup> %	Bp (mm) or mp, °C	<i>n</i> <sub>D</sub> (°C) or recrystn solvent	Formula	Analyses	Antiviral act. <sup>c</sup>	
20	N(CH <sub>3</sub> ) <sub>2</sub>	D	40	83-85 (0.1)	1.4714 (26)	C <sub>10</sub> H <sub>21</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	++	
21	N[CH(CH <sub>3</sub> ) <sub>2</sub> ] <sub>2</sub>	B	76	106-111 (0.07)	1.4721 (24)	C <sub>14</sub> H <sub>29</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	++	
22	N[(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub> ] <sub>2</sub>	B	24	146-148 (1.0)	1.4679 (25)	C <sub>16</sub> H <sub>33</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	-	
23	N(CH <sub>3</sub> )CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	B	79	157 (0.25)	1.5209 (24)	C <sub>16</sub> H <sub>25</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	-	
24	N(CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>		62	208-209 (0.1)	1.5529 (23)	C <sub>22</sub> H <sub>29</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	-	
25	2HCl·N(C <sub>2</sub> H <sub>5</sub> )-1-C <sub>10</sub> H <sub>15</sub> <sup>d</sup>		13	227-229		C <sub>26</sub> H <sub>37</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>2</sub> ·H <sub>2</sub> O	C, H, N	-	
26	N(C <sub>2</sub> H <sub>5</sub> )C <sub>6</sub> H <sub>5</sub>	C	39	156 (0.25)	1.5434 (27)	C <sub>16</sub> H <sub>25</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	-	
27	N(C <sub>2</sub> H <sub>5</sub> )CH <sub>2</sub> CF <sub>3</sub>	B	72	85-88 (0.05)	1.4407 (25)	C <sub>12</sub> H <sub>22</sub> F <sub>3</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	-	
28		B <sup>e</sup>	79	118-126 (0.15)	1.4903 (24)	C <sub>13</sub> H <sub>25</sub> N <sub>3</sub> O <sub>2</sub>	C, H; N <sup>g</sup>	++	
29		B	56	135-137 (0.25)	1.4913 (24)	C <sub>12</sub> H <sub>23</sub> N <sub>3</sub> O <sub>3</sub>	C, H, N	+	
30		B	29	112-114 (0.1)	1.4900 (26)	C <sub>12</sub> N <sub>3</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	+	
31	N(CH <sub>3</sub> ) <sub>2</sub> <sup>f</sup>	B	77	130-132 (0.1)	1.4934 (25)	C <sub>13</sub> H <sub>26</sub> N <sub>4</sub> O <sub>2</sub>	C, H, N	-	
33	2HCl·NHCH <sub>3</sub>		54	212-213	EtOH	C <sub>9</sub> H <sub>21</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>2</sub>	H, N; C <sup>h</sup>	-	
34	2HCl·NHCH <sub>2</sub> -		68	232-233	EtOH	C <sub>15</sub> H <sub>31</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	-	
35	CH(CH <sub>3</sub> ) <sub>2</sub>	B	57	77-78 (0.1)	1.4627 (23)	C <sub>11</sub> H <sub>22</sub> N <sub>2</sub> O <sub>2</sub>	C, H, N	-	
36	OCH <sub>2</sub> CH <sub>3</sub>	D	64	108 (1.3)	1.4644 (24)	C <sub>10</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub>	C, H, N	-	
37	SCH <sub>2</sub> CH <sub>3</sub>	B	49	112 (0.05)	1.4999 (26)	C <sub>10</sub> H <sub>20</sub> N <sub>2</sub> O <sub>2</sub> S	C, H, N	-	

<sup>a-c</sup> See corresponding footnotes in Table I. <sup>d</sup> C<sub>10</sub>H<sub>15</sub> = adamantyl. <sup>e</sup> When **28** was prepared in a manner similar to that for **68**, *i.e.*, higher reaction temperature, a by-product was bis-N-2-piperidinoethyl ether, bp 97° (0.07 mm), *n*<sub>D</sub><sup>20</sup> 1.4811. *Anal.* (C<sub>14</sub>H<sub>28</sub>N<sub>2</sub>O) C, H, N. <sup>f</sup> The starting material for **31** was 1-(2-hydroxyethyl)-4-methylpiperazine for the synthesis of which see J. Cymerman-Craig, R. J. Harrison, M. E. Tate, R. H. Thorp, and R. Ladd, *Australian J. Chem.*, **9**, 89 (1956). <sup>g</sup> N: calcd, 16.5; found, 16.0 <sup>h</sup> C: calcd, 39.4; found, 40.0.

change methods, it required no excess of the amino alcohol. It was successful with dialkylamino alcohols in which the amino and hydroxyl groups were separated by three or more atoms and with  $\beta$ -amino alcohols when

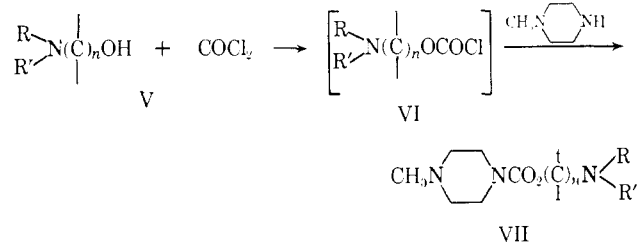
the amine was aromatic, a pyridine derivative, or part of an alicyclic ring. However, with simple  $\beta$ -dialkylaminoethanols procedure C was unsatisfactory, due either to a cyclization-dealkylation reaction leading to

TABLE III  


No.	R'	Method <sup>a</sup>	Yield, <sup>b</sup> %	Bp (mm) or mp, °C	n <sub>D</sub> <sup>20</sup> (°C) or recrystn solvent	Formula	Analyses	Antiviral act. <sup>c</sup>
38	(CH <sub>2</sub> ) <sub>3</sub> N(CH <sub>3</sub> ) <sub>2</sub>	B	41	114 (0.7)	1.4770 (23)	C <sub>11</sub> H <sub>23</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	±
39	(CH <sub>2</sub> ) <sub>3</sub> N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	B	29	126-128 (0.9)	1.4712 (25)	C <sub>14</sub> H <sub>27</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	+
40	(CH <sub>2</sub> ) <sub>4</sub> N(CH <sub>3</sub> ) <sub>2</sub> <sup>d</sup>	C	11	126 (2.5)	1.4688 (28)	C <sub>12</sub> H <sub>25</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	-
41	(CH <sub>2</sub> ) <sub>5</sub> N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	C	35	140 (0.45)	1.4712 (26)	C <sub>15</sub> H <sub>31</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	-
42	(CH <sub>2</sub> ) <sub>5</sub> O(CH <sub>2</sub> ) <sub>2</sub> N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	C	49	130-132 (0.2)	1.4710 (25)	C <sub>14</sub> H <sub>29</sub> N <sub>3</sub> O <sub>3</sub>	C, H, N	-
43	CH(CH <sub>3</sub> )CH <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	D	35	106 (1.6)	1.4662 (25)	C <sub>11</sub> H <sub>23</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	++
44	CH(CH <sub>3</sub> )CH <sub>2</sub> N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	D	35	92-95 (0.03)	1.4686 (23)	C <sub>13</sub> H <sub>27</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	+++
45	CH(CH <sub>3</sub> )CH <sub>2</sub> N(C <sub>3</sub> H <sub>7</sub> ) <sub>2</sub>	B	76	106-108 (0.05)	1.4643 (25)	C <sub>15</sub> H <sub>31</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N <sup>e</sup>	+++
46	CH(CH <sub>3</sub> )CH <sub>2</sub> N 	B	83	115-118 (0.01)	1.4825 (24)	C <sub>14</sub> H <sub>27</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	-
47	CH(CH <sub>2</sub> ) <sub>3</sub> N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	C	15	100-102 (0.04)	1.4668 (26)	C <sub>15</sub> H <sub>31</sub> N <sub>3</sub> O <sub>2</sub>	H, N; C <sup>f</sup>	-
48		B	64	95-97 (0.06)	1.4753 (27)	C <sub>12</sub> H <sub>25</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	-
49	 (trans)	B	58	108 (0.04)	1.4879 (21)	C <sub>14</sub> H <sub>25</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	-
50	CHCH(CH <sub>3</sub> )N(CH <sub>3</sub> ) <sub>2</sub> <sup>g</sup>   C <sub>6</sub> H <sub>5</sub> (erythro)	D	40	148-151 (0.15)	1.5198 (25)	C <sub>17</sub> H <sub>27</sub> N <sub>3</sub> O <sub>2</sub>		±
51		C	51	114-115 (0.07)	1.4892 (26)	C <sub>12</sub> H <sub>21</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	++
52		C	45	124 (0.8)	1.4878 (26)	C <sub>12</sub> H <sub>21</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	+
53		C	72	129 (0.07)	1.5079 (25)	C <sub>14</sub> H <sub>25</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	-
54	CH[CH <sub>2</sub> N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> ] <sub>2</sub>	E	6	132 (0.5)	1.4752 (23)	C <sub>17</sub> H <sub>36</sub> N <sub>4</sub> O <sub>2</sub>	H, N; C <sup>f</sup>	-
55		C	30	95-97	Heptane	C <sub>14</sub> H <sub>29</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	-
56	CH <sub>2</sub> CH <sub>2</sub> - 	E	9	146 (5)	1.5220 (22)	C <sub>13</sub> H <sub>23</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	-
57	CH <sub>2</sub> - 	C	34	134 (0.1)	1.5279 (25)	C <sub>12</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	-
58		C	8	126 (0.1)	1.5323 (28)	C <sub>11</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	-
59	C <sub>6</sub> H <sub>5</sub> NO <sub>2</sub> ·p·HCl		80	232-236	EtOH	C <sub>13</sub> H <sub>16</sub> ClN <sub>3</sub> O <sub>4</sub>	C, H, N	-
60	CH <sub>2</sub> CH=CH <sub>2</sub>	B	28	63-65 (0.1)	1.4760 (25)	C <sub>8</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub>	C, H, N	-
61	CH <sub>2</sub> CH <sub>2</sub> Cl·HCl <sup>h</sup>		73	160-162	EtOH-EtOAc			-

<sup>a</sup> See corresponding footnotes in Table I. <sup>d</sup> The starting material for **40** was 4-dimethylaminobutanol for the synthesis of which see E. Szervasi, *Bull. Soc. Chim. France*, 647 (1949). <sup>e</sup> The precursor of **49** was XXII. See Experimental Section. <sup>f</sup> See Experimental Section for precursor XXIII. <sup>g</sup> N: calcd, 14.7; found, 14.2. <sup>h</sup> C: calcd, 63.1; found, 62.6. <sup>i</sup> C: calcd, 62.1; found, 61.5. <sup>j</sup> For synthesis of **61** see ref 11.

oxazolidinones<sup>4</sup> or to the production of a  $\beta$ -dialkylaminoethyl chloride, possibly *via* an ethylenimmonium intermediate.<sup>4</sup> In retrospect, the information disclosed in ref 4 would suggest that a slight change in the reaction conditions of procedure C as outlined in the Experimental Section of this paper might permit the use of this procedure even with  $\beta$ -dialkylaminoethanols.



A third method for the preparation of compounds of this class consisted of the reaction of 4-methylpiperazine-1-carbonyl chloride<sup>5</sup> with either the sodium salt of the required amino alcohol (procedure D) or the amino alcohol itself (procedure E).

**Variations in b (Tables IV and V).**—Replacements of either one or both of the oxygens of **1** by sulfur, nitrogen, or carbon are listed in Table IV. Changes in the piperazine portion of the molecule are tabulated in Table V.

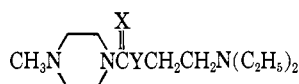
While testing other compounds related to **1** it was noted that 1,1'-carbonylbis-4-methylpiperazine dihydrochloride (**77**) exhibited an interesting antiviral activity. Table VI lists compounds related to **77** and containing two or more N-methylpiperazine units.

**Antiviral Testing.**—The antiviral testing was carried out by Mr. H. F. Lindh of these laboratories by a procedure similar to that previously described.<sup>2</sup> Male

(4) K. C. Murdock, *J. Org. Chem.*, **33**, 1367 (1968).

(5) H. Morren, S. Trolin, R. Denayer, and E. Grivsky, *Bull. Soc. Chim. Belges*, **59**, 228 (1950).

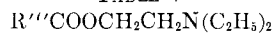
TABLE IV

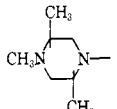
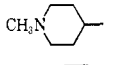
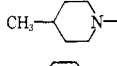
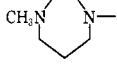
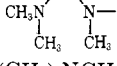




No.	X	Y	Method <sup>a</sup>	Yield, <sup>b</sup> %	Bp (mm) or mp, °C	<i>n</i> <sub>D</sub> (°C) or recrystn solvent	Formula	Analyses	Antiviral act. <sup>c</sup>
62	O	NH <sup>d</sup>	E	16	122–124 (0.1)	1.4928 (26)	C <sub>12</sub> H <sub>26</sub> N <sub>4</sub> O	H, N; C <sup>f</sup>	–
63	O	NCH <sub>3</sub> <sup>e</sup>	E	23	102 (0.1)	1.4889 (24)	C <sub>11</sub> H <sub>24</sub> N <sub>4</sub> O <sup>e</sup>	C, H, N	–
64	O	S·2HCl	D	56	229–234 dec	EtOH–Et <sub>2</sub> O	C <sub>12</sub> H <sub>26</sub> N <sub>3</sub> OS·2HCl	C, H, N, S	+
65	S	O·2HCl		26	162–163 dec	EtOH	C <sub>12</sub> H <sub>26</sub> N <sub>3</sub> OS·2HCl	C, H, N, Cl	–
66	S	S·2HCl		22	232–236 dec	EtOH	C <sub>12</sub> H <sub>26</sub> N <sub>3</sub> S <sub>2</sub> ·2HCl	C, H, N, Cl	–

<sup>a–c</sup> See corresponding footnotes in Table I. <sup>d</sup> See H. Morren, S. Trolin, R. Denayer, and E. Grinsky, *Bull. Soc. Chim. Belges*, **59**, 226 (1950); *Chem. Abstr.*, **45**, 6211b (1951). <sup>e</sup> Compound **63** was a dimethylaminoethyl derivative. <sup>f</sup> C: calcd, 59.5; found, 59.0.

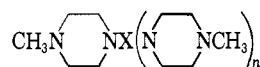
TABLE V





No.	R'''	Method <sup>a</sup>	Yield, <sup>b</sup> %	Bp (mm) or mp, °C	<i>n</i> <sub>D</sub> (°C)	Formula	Analyses	Antiviral act. <sup>c</sup>
68			23	118–119 (0.6)	1.4690 (28)	C <sub>14</sub> H <sub>29</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	+
69		D <sup>d</sup>	18	84–86 (0.05)	1.4622 (22)	C <sub>13</sub> H <sub>26</sub> N <sub>2</sub> O <sub>2</sub>	C, H, N	–
70		D <sup>e</sup>	61	129–130 (3.7)	1.4658 (22)	C <sub>13</sub> H <sub>26</sub> N <sub>2</sub> O <sub>2</sub>	C, H, N	–
71		B <sup>f</sup>	62	106–109 (0.05)	1.4763 (24)	C <sub>13</sub> H <sub>27</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	–
72		E <sup>g</sup>	24	82 (0.05)	1.4542 (25)	C <sub>12</sub> H <sub>27</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	–
73	(CH <sub>3</sub> ) <sub>2</sub> NCH <sub>2</sub> CH <sub>2</sub> O <sup>h</sup>		58	63 (0.07)	1.4351 (24)	C <sub>9</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub>	C, N; H <sup>k</sup>	–
74	[(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> NCH <sub>2</sub> CH <sub>2</sub> ] <sub>2</sub> N	D <sup>i</sup>	36	130–135 (0.05)	1.4593 (24)	C <sub>19</sub> H <sub>42</sub> N <sub>4</sub> O <sub>2</sub>	C, H, N	–
75	(CH <sub>3</sub> ) <sub>2</sub> N(CH <sub>2</sub> ) <sub>3</sub> N 		13	93 (0.02)	1.4529 (28)	C <sub>13</sub> H <sub>25</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	–
76	(CH <sub>3</sub> ) <sub>2</sub> N 	D <sup>j</sup>	80	55–65 (0.1)	1.4426 (24)	C <sub>9</sub> H <sub>20</sub> N <sub>2</sub> O <sub>2</sub>	C, H, N	–

<sup>a</sup> The methods are detailed in the Experimental Section. However for this table the starting materials are different as indicated in succeeding footnotes. <sup>b,c</sup> See corresponding footnotes in Table I. <sup>d</sup> The precursor of **69** was XIII. See Experimental Section. <sup>e</sup> The precursor of **70** was XIV. <sup>f</sup> The precursor of **71** was XVI. <sup>g</sup> The precursor of **72** was XVII. <sup>h</sup> This was actually a dimethylamino derivative, *i.e.*, bis(dimethylaminoethyl) carbonate. <sup>i</sup> The precursor of **74** was XVIII. <sup>j</sup> Prepared by the method of ref 16. <sup>k</sup> H: calcd, 9.9; found, 9.2.

TABLE VI



No.	X	<i>n</i>	Method <sup>a</sup>	Yield, <sup>b</sup> %	Bp (mm) or mp, °C	<i>n</i> <sub>D</sub> (°C) or recrystn solvent	Formula	Analyses	Antiviral act. <sup>c</sup>
77	>CO·2HCl	1		70	304–305 dec	...	C <sub>11</sub> H <sub>24</sub> Cl <sub>2</sub> N <sub>4</sub> O	C, H, N	++
78	>SO <sub>2</sub> ·2HCl <sup>d</sup>	1		62	260 dec	EtOH	C <sub>10</sub> H <sub>24</sub> ClN <sub>4</sub> O <sub>2</sub> S·H <sub>2</sub> O	C, H, S, Cl	++
79	>C=S·2HCl <sup>f</sup>	1							–
80	CH <sub>2</sub> <sup>g</sup>	1		64	140 (16)	1.4855 (24)	C <sub>11</sub> H <sub>24</sub> N <sub>4</sub>	C, H, N	–
81	>P=O trimalate	2	F	21	189–190	EtOH	C <sub>27</sub> H <sub>45</sub> N <sub>6</sub> O <sub>13</sub> P	H, N; C <sup>e</sup>	–
82		1	F	24	160–162 (1.0)	1.5050 (25)	C <sub>11</sub> H <sub>25</sub> N <sub>4</sub> OP· <sup>2</sup> / <sub>3</sub> H <sub>2</sub> O	C, H, N	–
83		1	F	35	184–185	EtOH	C <sub>24</sub> H <sub>35</sub> N <sub>4</sub> O <sub>9</sub> P	C, H, N	–
84	COCO	1		46	130–132	Heptane	C <sub>12</sub> H <sub>22</sub> N <sub>4</sub> O <sub>2</sub>	C, H, N	–

<sup>a–c</sup> See corresponding footnotes in Table I. <sup>d</sup> The free base was prepared as described in ref 9 and converted to its salt using ethanolic HCl. <sup>e</sup> C: calcd, 46.8; found, 46.1. <sup>f</sup> See R. E. Orth, *J. Pharm. Sci.*, **53**, 1261 (1964). <sup>g</sup> Prepared as described by O. Hromatka, G. Stehlik, and F. Sauter, *Monatsh. Chem.*, **91**, 107 (1960).

white mice, weighing 18–20 g each, were infected by the intranasal instillation of an LD<sub>95</sub> dose of Influenza A (PR8) virus. The compound was administered orally in a single maximum-tolerated dose immediately after infection. Each compound was first tested in five mice. If less than two mice survived the 14-day test period the compound was rejected as inactive. If two or more

mice survived, the compound was retested in ten mice. Test results are listed in Tables I–VII where ++ = 60–80% survival, + = 35–60% survival, and – = rejected as inactive. Of the compounds tested 19 were accepted as active. Further evaluation of the active compounds showed that none was superior to 2-diethylaminoethyl 4-methylpiperazine-1-carboxylate (**1**).<sup>2</sup>



then evaporated at aspirator pressure on a steam bath. The residue was distilled through a spinning band fractionation column.

**Procedure B.**<sup>8</sup>—A solution of 0.10 mole of ethyl 4-methylpiperazine-1-carboxylate,<sup>9</sup> 0.40 mole of the amino alcohol, and 1.0 g of NaOMe was heated under reduced pressure for *ca.* 9 hr using an oil bath kept at temperatures ranging from 85–125°; the mixture was stirred magnetically under a spinning band fractionating column. The exact temperature and pressure depended upon the boiling point of the alcohol. For example with higher boiling amino alcohols the bath was kept at 85–95° for 3 hr, 95–100° for 3 hr, and 100–125° for 3 hr, all at a pressure of 15 mm. During this procedure EtOH and some of the amino alcohol distilled. For lower boiling alcohols somewhat lower temperatures and higher pressures were used. The main consideration is to keep the temperature low enough to avoid the ether by-product which is formed at higher temperatures. The material remaining in the flask was then fractionated using a spinning band column.<sup>10</sup>

**Procedure C.**—A stirred solution of COCl<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub> (100 ml, 2 moles) was kept at <math>\leq -30^\circ</math> during the gradual addition of a solution of 0.10 mole of the amino alcohol in 50 ml of CH<sub>2</sub>Cl<sub>2</sub>. The cooling bath was removed and the mixture was allowed to stand at 25° for 30–50 hr. (A standing time of only about 20 min at 25° would probably have been preferable in this and analogous syntheses, in accord with the comments in the discussion section, allowing reaction even with  $\beta$ -dialkylamino alcohols.<sup>4</sup> Solvent was removed by evaporation at <math>\leq 50^\circ</math>, repeating the evaporation with more CH<sub>2</sub>Cl<sub>2</sub> to assure removal of unreacted COCl<sub>2</sub>. A solution of the residual syrup in 100 ml of CH<sub>2</sub>Cl<sub>2</sub> was kept at about 25° (ice bath, stirring) during the addition of 15.0 g (0.15 mole) of 1-methylpiperazine in 50 ml of CH<sub>2</sub>Cl<sub>2</sub>. After 20–40 hr it was evaporated to dryness. A solution of the residue in a minimum of H<sub>2</sub>O (20 ml) was chilled and swirled during successive additions of KOH (22.44 g, 0.4 mole). The resulting thick slurry was extracted in the round-bottomed, 500-ml reaction flask with 100 ml, then three 40-ml portions of ether, decanting the extracts. The extracts were dried (K<sub>2</sub>CO<sub>3</sub>), filtered, and evaporated. Fractional distillation of the residue gave the product.

**Procedure D.**—To the amino alcohol (0.40 mole) or thiol in 50 ml of C<sub>6</sub>H<sub>6</sub> or (CH<sub>3</sub>OCH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>O was added Na (4.6 g, 0.20 g-atom). This was heated to reflux until solution was complete and then cooled to room temperature. 4-Methylpiperazine-1-carbonyl chloride hydrochloride<sup>5</sup> (22.5 g, 0.11 mole) was added and the mixture was stirred at room temperature for 3 min, refluxed for 2 hr, cooled, and filtered. Removal of the solvent and the excess amino alcohol was carried out at reduced pressure on a steam bath and the residue was distilled.

**Procedure E.**—A stirred suspension of 19.9 g (0.1 mole) of 4-methylpiperazine-1-carbonyl chloride hydrochloride<sup>5</sup> in 100 ml of CH<sub>2</sub>Cl<sub>2</sub> was chilled with an ice bath during the gradual addition of a solution of 0.15 mole of the alcohol or amine in 50 ml of CH<sub>2</sub>Cl<sub>2</sub>. The mixture was stirred at room temperature for 5 days and then worked up as in procedure C. In this procedure one of the fractions collected during distillation often crystallized in the receiver. Its spectrum showed it to be predominantly 1,1'-carbonylbis-4-methylpiperazine (77).

**Procedure F.**—To a well-stirred solution of 15.0 g (0.15 mole) of N-methylpiperazine in 50 ml of CHCl<sub>3</sub> was added slowly with cooling (0–5°) 40 ml of CHCl<sub>3</sub> containing an acid chloride in an amount (0.05 or 0.075 mole) calculated to prepare the desired product. The reaction mixture was heated to reflux for 18 hr after which time the solvent was removed by evaporating. The residue was dissolved in 30 ml of H<sub>2</sub>O, chilled, and swirled during the gradual addition of 40 g of KOH. The slurry was extracted with three 100-ml portions of ether. The ether solution was dried (MgSO<sub>4</sub>) and the solvent was evaporated. The product

was then either distilled or converted to a maleate salt using an Me<sub>2</sub>CO solution of maleic acid.

**Thiosemicarbazone of 2-Diethylaminoethyl 4-Acetyl-piperazine-1-carboxylate (13).**—2-Diethylaminoethyl 4-acetyl-piperazine-1-carboxylate (12) (1.0 g, 3.5 mmoles), 320 mg (3.5 mmoles) of thiosemicarbazide, 20 ml of EtOH, and one drop of concentrated HCl were mixed and heated on a steam bath for 7 hr. The solution was evaporated to dryness and the residue was slurried in ether and cooled. A white crystalline product was collected leaving some gummy product behind; yield 400 mg, mp 133–136°. This was recrystallized from EtOH–Et<sub>2</sub>O (1.5:2). See Table I for physical data.

**2-Diethylaminoethyl 4-Maleimidomethylpiperazine-1-carboxylate Dihydrochloride (14).**—A solution of 6.8 g (53.5 mmoles) of N-hydroxymethylmaleimide in 120 ml of C<sub>6</sub>H<sub>6</sub> was heated to reflux using a Dean–Stark water take-off. To this was added dropwise over a 30-min period a solution of 12.2 g (53.5 mmoles) of 2-diethylaminoethyl piperazine-1-carboxylate (2) in 30 ml of C<sub>6</sub>H<sub>6</sub>. The solution was refluxed 45 min longer, then cooled and filtered to remove a little polymeric material. The filtrate was evaporated to a syrup which was redissolved in 40 ml of EtOH. (Attempts to obtain a crystalline free base were unsuccessful.) This solution was treated with 22 ml of 6 N ethanolic HCl and cooled to give a crystalline product; yield 11.5 g. The product was recrystallized from 45 ml of EtOH and then again from 220 ml of MeCN to give a nicely crystalline product.

**2-Diethylaminoethyl 4-Formylpiperazine-1-carboxylate (15).**—A solution of 11.5 g (0.05 mole) of 2-diethylaminoethyl piperazine-1-carboxylate (2) and 40 ml of 97% HCOOH was heated on a steam bath for 1.75 hr. The solution was evaporated to a small volume, EtOAc was added, and the evaporation was repeated. The residue was dissolved in 10 ml of H<sub>2</sub>O and cooled in an ice bath and 10 ml of 50% NaOH was added. The mixture was extracted twice with ether, and the ether was dried (MgSO<sub>4</sub>) and then evaporated to a syrup. The syrup was fractionated using a spinning band column. The first fraction was discarded and the product was then collected.

**2-Diethylaminoethyl 4-Nitrosopiperazine-1-carboxylate (16).**—A mixture of 68.7 g (0.3 mole) of 2-diethylaminoethyl piperazine-1-carboxylate (2), 160 g of ice, and 100 ml of concentrated HCl, cooled in an ice bath to about 0°, was stirred during the slow, dropwise addition of a solution of 41.5 g (0.6 mole) of NaNO<sub>2</sub> in about 70 ml of H<sub>2</sub>O. The resulting solution was made alkaline with 110 ml of cold 10 N NaOH. The product separated as a liquid and was extracted with three portions of ether. The ether solution was dried (MgSO<sub>4</sub>) and then evaporated to give the product, 65 g (83%). A portion of this material (10.7 g) was distilled to give pure product; yield 8.2 g.

**2-Diethylaminoethyl 4-Aminopiperazine-1-carboxylate (17).**—A mixture of 55 g (0.21 mole) of 2-diethylaminoethyl 4-nitrosopiperazine-1-carboxylate (16) (undistilled material; see above preparation), 90 g of Zn dust, and 200 ml of H<sub>2</sub>O was stirred vigorously at 25–30° while 170 ml of 85% AcOH was added dropwise over a 1.5-hr period. This was then warmed to 50° for 1 hr with stirring, and then filtered. The solution upon cooling, gave a crystalline product [Zn(OAc)<sub>2</sub>] which was removed by filtration. The filtrate was cooled, stirred, and carefully made alkaline by the addition of about 240 ml of 10 N KOH. This mixture was extracted seven times with 200-ml portions of ether. The ether solution was dried (MgSO<sub>4</sub>), the ether was removed by distillation, and the remaining liquid was fractionated. After a forerun had been discarded the product was collected.

**2-Diethylaminoethyl 4-Carbamylpiperazine-1-carboxylate (18).**—2-Diethylaminoethyl piperazine-1-carboxylate (11.5 g, 0.05 mole), 40 ml of AcOH, and 4.5 g (0.055 mole) of potassium cyanate were mixed without cooling and warmed on a steam bath until all the solid was dissolved (about 5 min). Some excess AcOH was removed on the steam bath under reduced pressure at the water pump (10–15 min). The residue was dissolved in H<sub>2</sub>O which was then cooled and made alkaline with 30 ml of 10 N NaOH. This was extracted with three 50-ml portions of CHCl<sub>3</sub>. The CHCl<sub>3</sub> solution was dried (MgSO<sub>4</sub>) and evaporated to an oil which was dissolved in ether. The solution quickly deposited a crystalline solid; yield 8.0 g (59%), mp 84–85°. A portion of this material (1.2 g) was dissolved in 2 ml of CHCl<sub>3</sub> and 10 ml of ether was then added; yield 1.0 g.

**2-Dibenzylaminoethyl 4-Methylpiperazine-1-carboxylate (24).**—A solution of 38.6 g (0.16 mole) of dibenzylaminoethanol and 1.54 g (0.03 mole) of NaOMe in 27.6 g (0.16 mole) of ethyl 4-methylpiperazine-1-carboxylate<sup>9</sup> was heated under reflux, using

(8) A few of the low yields reported for procedure B in the tables were actually obtained using the higher reaction temperatures described in the Discussion. A more strict adherence to the temperatures described in procedure B would undoubtedly increase the yield in those cases.

(9) H. W. Stewart, R. J. Turner, J. J. Denton, S. Koshner, L. M. Brancome, W. L. McEwan, R. I. Hewitt, and Y. Subbarow, *J. Org. Chem.*, **13**, 134 (1948).

(10) In some experiments the separation of solid (sodium salts) made it necessary to slurry with ether and remove the salts by filtration before final distillation.

an oil bath at 103–108°, a spinning band column, and the vacuum of an oil pump. During 105 min the pressure gradually fell from 3.0 to 0.10 mm, when the pot contents had stopped bubbling. After heating for another 0.5 hr at 0.09 mm, the very viscous material in the still pot was diluted with 100 ml of ether and chilled. Sodium alkoxide was neutralized by the dropwise addition of a solution of 1.43 g of 95.9%  $H_2SO_4$  in 10 ml of ether. The resulting mixture was very thick, but after gentle warming a sudden coagulation occurred. After addition of more ether the solid was removed by filtration (Celite), the ether was removed by evaporation, and the residue was distilled without fractionation in the "air bath chimney" apparatus described in the procedure used for **96**. The product was 36.3 g (65%) of a very viscous, yellow oil.

**1-Ethylaminoadamantane Hydrochloride (IX).**—A solution of 1-acetamidoadamantane (15.8 g, 0.082 mole) in 100 ml of dry THF was added to a stirred suspension of  $LiAlH_4$  (7.2 g, 0.2 mole) in 200 ml of dry THF over a 40-min period. The mixture was refluxed for 6.0 hr, then cooled in an ice bath and treated carefully with 7.6 ml of  $H_2O$ , 23 ml of 15% NaOH, and finally 23 ml of  $H_2O$ . The precipitated solid was collected and washed with 100 ml of THF. The filtrate was evaporated to an oil and dissolved in 200 ml of 5% HCl. The acid solution was extracted with two 100-ml portions of EtOAc (discarded) then basified with 50 ml of 10 N NaOH to give a crystalline solid; yield 12 g. For analysis a small portion of the material was converted to the hydrochloride salt (mp 325–327° dec). *Anal.* ( $C_{12}H_{23}ClN$ ) C, H, Cl, N.

**N-(1-Adamantyl)-N-ethylaminoethanol (XI).**—N-Ethylaminoadamantane (IX) (10 g, 0.056 mole) and ethylene bromohydrin (7.0 g, 0.056 mole) were added to 20 ml of MeOH and refluxed overnight. The solvent was removed at reduced pressure and the residue was slurried in 100 ml of 1 N NaOH. This was extracted with three 100-ml portions of ether which were combined and dried ( $MgSO_4$ ). The ether was evaporated and the residue was distilled; yield 3.3 g; bp 100–101° (0.04 mm). *Anal.* ( $C_{14}H_{25}NO$ ) C, H, N.

**2-[[1-(Adamantyl)ethylamino]ethyl 4-Methylpiperazine-1-carboxylate Dihydrochloride (25).**—N-(1-Adamantyl)-N-ethylaminoethanol (XI) (3.2 g, 14.4  $\mu$ moles) was added to 50 ml of dry  $C_6H_6$  containing 0.5 g (21.7  $\mu$ -atoms) of Na and refluxed overnight. The mixture was chilled and a solution of 4-methylpiperazine-1-carboxyl chloride [prepared from 3.5 g (17  $\mu$ moles) of the hydrochloride<sup>9</sup>] in 35 ml of toluene was added, then stirred at room temperature for 0.5 hr. After having been heated on a steam bath for 2.0 hr the reaction mixture was cooled and filtered, and the filtrate was evaporated at reduced pressure. The resulting oily residue was taken up in about 5.0 ml of petroleum ether (bp 30–60°) and chilled to afford 0.5 g of 1,1'-carbonylbis-4-methylpiperazine. The filtrate was evaporated to dryness and the residue was slurried in 25 ml of  $H_2O$  containing 1.0 ml of 10 N NaOH, then extracted with three 50-ml portions of ether. The combined ether extracts were extracted with three 100-ml portions of  $H_2O$ , dried ( $MgSO_4$ ), and evaporated to an oil; yield 2.9 g. Thin layer chromatography indicated this product was predominantly a mixture of two compounds, one of which was the starting amino alcohol. This crude product was chromatographed on Florisil to afford the desired compound which was converted to a crystalline hydrochloride; yield 787 mg, mp 227.5–229° dec. The structure of this product was confirmed by ir and nmr spectroscopy.

**2-Methylaminoethyl 4-Methylpiperazine-1-carboxylate Dihydrochloride (33).**—A solution of 17.5 g (0.06 mole) of 2-(N-benzyl-N-methylamino)ethyl 4-methylpiperazine-1-carboxylate (**23**) in 100 ml of absolute EtOH and 21.0 ml of 6 N absolute ethanolic HCl was shaken in a Parr hydrogenation apparatus with 1.75 g of a 10% Pd-C catalyst. After 2.0 hr the hydrogen pressure had fallen only from 35.0 to 34.6 psi, all in the first 4 min. So 1.75 g of platinum oxide catalyst was added. Hydrogen uptake ceased within 20 hr, when almost 3 mole equiv (ca. 0.17 mole) of hydrogen had been used. Much solid had separated. This solid dissolved after the addition of 15 ml of  $H_2O$ . The catalysts were removed by filtration, and the filtrate and 95% ethanolic washes were evaporated. The residual syrup was dried by dissolving it in 50 ml of EtOH and 15 ml of  $C_6H_6$ , then evaporating this solution. The residual white solid was washed with EtOH; yield 11.27 g, mp 208–212° dec. Recrystallization from 275 ml of EtOH returned 8.81 g (54%) of a white solid.

**2-[[Cyclohexylmethylamino]ethyl 4-Methylpiperazine-1-carboxylate Dihydrochloride (34).**—A solution of 29.4 g (0.08 mole) of 2-dibenzylaminoethyl 4-methylpiperazine-1-carboxylate (**24**)

in 130 ml of 95% EtOH was cooled during the addition of 14 ml of concentrated HCl. Hydrogenation with 2.94 g of PtO<sub>2</sub> catalyst in a Parr shaker with an initial pressure of 2.46 kg/cm<sup>2</sup> was continued for 21.6 hr. The product remained in solution. (Compare the separation of product in the hydrogenation leading to **33**, where  $H_2O$  was absent.) Catalyst was removed by filtration and washed with 90% EtOH. Evaporation of the filtrate left a residue which was dried twice by dissolving it in 50 ml of EtOH, adding 15 ml of  $C_6H_6$ , and evaporating to dryness. Crystallization of the resulting gum from EtOH, finally at –5°, gave 15.1 g of white solid, mp 232–233° dec. Recrystallization from *n*-PrOH (not recommended) returned 12.76 g of white solid, mp 228–229° dec. Unlike the starting material or **23** the product had an ir spectrum without any peak near 13.6  $\mu$ , indicating that a monosubstituted phenyl group was not present; peaks at 5.88 and 7.97  $\mu$  were normal for the urethan grouping of this series. In D<sub>2</sub>O the product had an nmr spectrum with no peaks below  $\tau$  5 (no aromatic CH); the peaks were at  $\tau$  5.33 (NH + 21H, 3 protons), 5.5–6.9 ( $CH_2$  adjacent to O or N, 14 protons), 7.00 ( $\geq N-CH_3$ , 3 protons), and 8.0–9.0 (cyclohexyl, 11 protons). The mother liquor of the original 15.1 g of product gradually deposited another 4.26 g of the same product.

***p*-Nitrophenyl 4-Methylpiperazine-1-carboxylate Hydrochloride (59).**—To a solution of *p*-nitrophenyl chloroformate (10.0 g, 0.05 mole) in 150 ml of anhydrous ether was added dropwise, with stirring, over 15 min, a solution of 4.0 g (0.04 mole) of N-methylpiperazine in 25 ml of anhydrous ether. The reaction mixture was stirred for an additional 30 min, then allowed to stand at room temperature overnight. The resulting cream-colored crystals were collected; yield 12.4 g, mp 222–232°. The crude product was recrystallized from 225 ml of EtOH using decolorizing charcoal to afford 9.7 g of product.

**2-Chloroethyl 4-Methylpiperazine-1-carboxylate Hydrochloride (61).**—To a solution of 2-chloroethyl chloroformate (14.3 g, 0.10 mole) in 150 ml of ether was added with stirring over a 1.5-hr period a solution of N-methylpiperazine (7.5 g, 0.075 mole) in 50 ml of ether. The reaction mixture was stirred at room temperature over the weekend and the product was collected by filtration; yield 17.6 g, mp 158–162°. This compound was dissolved in 50 ml of boiling EtOH, treated with Darco, and filtered. The filtrate was cooled and diluted with an equal volume of EtOAc. After the mixture had been chilled overnight the crystals were collected and dried; yield 13.3 g (73%), mp 160–162°.<sup>11</sup>

**4-Methylpiperazine-1-thiocarbonyl Chloride (XI).**—A solution of 43.6 g (0.436 mole) of N-methylpiperazine in 150 ml of  $C_6H_6$  was added over a 45-min period to a vigorously stirred solution of  $CS_2Cl_2$  (25 g, 0.218 mole) in 150 ml of toluene at –5°. After having been stirred for an additional 2 hr at room temperature the mixture was filtered and the solid was washed with  $C_6H_6$ . The filtrate was evaporated to remove solvent and the residue was washed with  $C_6H_6$ ; yield 12.1 g (31%), bp 98–110° (0.5–0.7 mm),  $n_D^{20}$  1.5879. *Anal.* ( $C_6H_{11}ClN_2S$ ) C, H, N, S.

**2-Diethylaminoethyl 4-Methylpiperazine-1-carbothionate Dihydrochloride (65).**—To a stirred solution of Na (1.54 g, 0.067  $\mu$ -atom) and diethylaminoethanol (7.85 g, 0.067 mole) in 50 ml of  $C_6H_6$  was added, over an 80-min period, a solution of 12.1 g (0.067 mole) of 4-methylpiperazine-1-thiocarbonyl chloride (XI) dissolved in 100 ml of  $C_6H_6$ . After having been stirred for an additional 2 hr at room temperature the reaction mixture was heated at 50–60° for 1.0 hr followed by 1.0 hr at 80°. The reaction mixture was cooled to room temperature and filtered from the precipitated salt and the filtrate was evaporated at reduced pressure. The residue was dissolved in 200 ml of anhydrous ether and saturated with anhydrous HCl to give a gum which was triturated to a solid with several fresh portions of ether.<sup>12</sup> The solid was crystallized from EtOH; yield 9.3 g, mp 162–165° dec. The addition of ether to the filtrate afforded a second crop; yield 2.0 g, mp 161–162.5° dec. These two crops were combined and recrystallized from EtOH using decolorizing charcoal; yield 5.9 g.

(11) Belgian Patent 619,225 (1962); *Chem. Abstr.*, **59**, (1524g) 01963i, gives mp 161.5–162°.

(12) Carbothionate **65** was converted to its hydrochloride without distillation because we had found that distillation caused an O to S rearrangement to the carbithiolate **64**. In this case the rearrangement is probably facilitated by the formation of a relatively stable ion pair similar to IIIA since ethyl 4-methylpiperazine-1-carbothionate does not rearrange under similar conditions. A similar rearrangement via a stabilized ion pair has been suggested by S. G. Jones, *Tetrahedron Letters*, 979 (1962).

**2-Diethylaminoethyl 4-Methylpiperazine-1-carbodithioate Dihydrochloride (66).**—Na (2.3 g, 0.10 g-atom) was dissolved in 25 ml of EtOH containing 10 g (0.10 mole) of N-methylpiperazine. To the resulting pasty solid was added 8.4 g (0.11 mole) of CS<sub>2</sub> with stirring over a 5.0-min period. A vigorous evolution of heat took place after which the reaction mixture was stirred for 15 min and then cooled to room temperature. Diethylaminoethyl chloride (11.0 ml) was added over a 7-min period with stirring, then heated at 55–60° for 1.0 hr. The mixture was cooled to room temperature and filtered and the filtrate was evaporated to an oil. The oil was distilled and the fraction boiling at 142.5–143° (0.06 mm) was collected; yield 8.0 g,  $n_D^{25}$  1.5640. This liquid was dissolved in 400 ml of ether and saturated with anhydrous HCl to give a gum which was crystallized from EtOH; yield 7.9 g.

**1-(4-Diethylaminobutyl)-4-methylpiperazine (67).**—A solution of 10.02 g (0.1 mole) of 1-methylpiperazine in 150 ml of 1,2-dichloroethane was chilled with an ice bath during the dropwise addition of 14.10 g (0.1 mole) of 4-chlorobutyl chloride. After another 15 min at 0° and 15 min at room temperature the mixture was chilled again during the gradual addition of 36.57 g (0.5 mole) of Et<sub>2</sub>NH. The mixture was heated under reflux for 25 hr and solvent was removed by evaporation. This reaction mixture was handled as in procedure A.

**2-Diethylaminoethyl trans-2,4,5-Trimethyl-1-piperazinecarboxylate (68) and 2,2''-Oxybistriethylamine (XII).**—A solution of 0.150 g of Na in 30 ml of 2-diethylaminoethanol was heated under reflux (bp ~68°) at aspirator pressure for 5.5 hr with 12.02 g of ethyl trans-2,4,5-trimethylpiperazine-1-carboxylate.<sup>13</sup> Ebullition with a slow stream of dried (Drierite tube) air removed by-product EtOH by entrainment. Heating under reflux was continued for another 14.5 hr at atmospheric pressure, ebullating with dry N<sub>2</sub>; the temperature of the reaction mixture gradually rose from 159 to 174°. Fractional distillation then gave 6.29 g of the desired urethan (68). See Table V for physical data. (The use of procedure B would almost certainly give a better yield.) An earlier cut from the distillation amounted to 4.43 g (34%), bp 97–100° (4 mm),  $n_D^{28}$  1.4389. Refractionation of this cut gave three cuts showing the presence of a small amount of a faster moving contaminant (by gas chromatography) followed by a final 0.40-g cut of a liquid, bp 98° (3 mm),  $n_D^{28}$  1.4379, which gave only a single peak on a gas chromatogram. *Anal.* (C<sub>11</sub>H<sub>23</sub>N<sub>2</sub>O) C, H, N. The retention time and ir spectrum were identical with those of an authentic sample of 2,2''-oxybistriethylamine (XII), bp 74° (0.08 mm),  $n_D^{27}$  1.4372, prepared<sup>14</sup> from 2-diethylaminoethyl chloride and sodium 2-diethylaminoethoxide.

**1-Methylpiperidine-4-carbonyl Chloride (XIII).**—A solution of 42.5 g (0.236 mole) of 1-methylpiperidine-4-carboxylic acid hydrochloride<sup>15</sup> in 230 ml of SOCl<sub>2</sub> was heated to reflux on a steam bath for 2 hr. The excess SOCl<sub>2</sub> was evaporated and the residue was evacuated under aspirator vacuum on a steam bath. The residue was slurried in warm ethylene chloride and allowed to stand at room temperature overnight. The solid was collected, washed with ethylene chloride, and dried over P<sub>2</sub>O<sub>5</sub> and KOH in a desiccator and then dried at 60°; yield 40 g.

**4-Methylpiperidine-1-carbonyl Chloride (XIV).**—The procedure was adapted from that described by Sekera, *et al.*,<sup>16</sup> for the synthesis of 2-diethylaminoethyl piperidinecarboxylate. To a solution of 0.6 mole of COCl<sub>2</sub> in 100 ml of CHCl<sub>3</sub> cooled with a Dry Ice–MeOH bath was gradually added a solution of 14.88 g (0.15 mole) of 4-methylpiperidine in 50 ml of CHCl<sub>3</sub>. The mixture was heated under reflux for 70 min, evaporated, then fractionated to give 20.39 g (84%) of the carbamoyl chloride, XIV, bp 98° (5 mm),  $n_D^{20}$  1.4857.

**Ethyl 1,4-Diazacycloheptane-1-carboxylate (XV).**—1,4-Diazacycloheptane dihydrobromide (56.2 g, 0.20 mole) was dissolved in 100 ml of H<sub>2</sub>O containing 8.2 g (0.10 mole) of NaOAc. To the stirred reaction mixture was added fourteen 0.96-ml portions (0.01 mole each) of ethyl chloroformate over 1.5 hr. After each addition of the chloroformate had dissolved, a solution of 0.82 g

(0.01 mole) of NaOAc in 3 ml of H<sub>2</sub>O was added. The mixture was chilled in an ice bath, 35 ml of 20% NaOH was added, and the total mixture was extracted with 100 ml of ether. Vapor phase chromatography indicated only low-boiling material was present in this extract. K<sub>2</sub>CO<sub>3</sub> (75 g) was added to the aqueous phase which was then extracted with three 200-ml aliquots of ether. The ether was removed after drying (MgSO<sub>4</sub>) to afford 18.6 g of product which was distilled; yield 16.2 g (47%), bp 64–67° (0.025 mm),  $n_D^{25}$  1.4788. *Anal.* (C<sub>8</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>) C, H, N.

**Ethyl 4-Methyl-1,4-diazacycloheptane-1-carboxylate (XVI).**—Ethyl 1,4-diazacycloheptane-1-carboxylate (XV) (16.2 g, 0.094 mole) dissolved in 6 ml of H<sub>2</sub>O was chilled in an ice-salt bath and 10 ml of 97% HCOOH was added. The solution was stirred at room temperature for 2 hr after the addition of 10 ml of 37% formaldehyde, then heated at 50–55° for 4 hr. The mixture was cooled in an ice bath and brought to pH 13.5 with 10 N NaOH (temperature kept below 10°) then extracted with three 100-ml portions of ether. The combined ether extracts were dried (MgSO<sub>4</sub>) and evaporated at reduced pressure and the residue distilled; yield 14.8 g (85%), bp 64.5–67° (0.06 mm),  $n_D^{28}$  1.4693. *Anal.* (C<sub>9</sub>H<sub>15</sub>N<sub>2</sub>O<sub>2</sub>) C, H, N: calcd, 15.0; found, 14.5.

**N-(2-Dimethylaminoethyl)-N-methylcarbamoyl Chloride Hydrochloride (XVII).**—A solution of 14.8 g (0.15 mole) of COCl<sub>2</sub> in 60 ml of CHCl<sub>3</sub> was agitated and kept at about –20° during the dropwise addition of a cold solution of 10.2 g (0.1 mole) of N,N,N'-trimethylethylenediamine in 25 ml of CHCl<sub>3</sub>. The resulting suspension was allowed to warm to 20°, then to stand for another 1 hr. Excess COCl<sub>2</sub> was removed by evaporation to dryness, repeating the evaporation with another 100 ml of CHCl<sub>3</sub>. This was used for the preparation of 72 (Table V).

**2-Dimethylaminoethyl Carbonate (73).**—To 50 ml of a 2 M solution of COCl<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub> kept at <–40° was gradually added a solution of 17.83 g (0.2 mole) of 2-dimethylaminoethanol in 100 ml of CH<sub>2</sub>Cl<sub>2</sub>. The reaction mixture was then allowed to stand for 3 days without further cooling. Much solid separated. A work-up as in general procedure A gave 11.9 g of a colorless liquid,  $\lambda_{\max}^{KBr}$  5.73 and 7.95  $\mu$ . See Table V for physical data.

**Bis-2-diethylaminoethylcarbamoyl Chloride Dihydrochloride (XVIII).**—Bis(2-diethylaminoethyl)amine<sup>17</sup> (21.5 g, 0.10 mole) dissolved in 50 ml of CHCl<sub>3</sub> was added during a 1.5-hr period to a stirred solution of 19.5 g (0.20 mole) of COCl<sub>2</sub> in 30 ml of CHCl<sub>3</sub> in an ice-salt bath. The reaction mixture was stirred an additional 0.5 hr at room temperature to give a homogeneous solution. Anhydrous HCl was bubbled into the solution whereupon two immiscible layers formed. The CHCl<sub>3</sub> layer was separated and discarded. The CHCl<sub>3</sub>-insoluble portion was extracted with 100 ml of CHCl<sub>3</sub> (discarded) and evaporated at reduced pressure to give dark crystals; yield 29 g.

**2-Diethylaminoethyl (3-Dimethylaminopropyl)methylcarbamate (75).**—To 50 ml of a 2 M solution of COCl<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub> kept at <–50° was added dropwise with swirling 0.1 mole (11.7 g) of 2-diethylaminoethanol (freshly distilled after drying over a little NaH). The resulting solution was warmed to just 20°, then kept at this temperature for just 5 min, using cold water to prevent any further rise in temperature. The solution was then kept at –30 to +10° during the addition of a solution of 11.6 g (0.1 mole) of N,N,N'-trimethyl-1,3-propanediamine in 50 ml of CH<sub>2</sub>Cl<sub>2</sub>. The mixture was stirred for 24 hr at ca. 24°. Crystalline material was removed by filtration and discarded. A work-up according to procedure A gave 1.7 g of a colorless liquid,  $\lambda_{\max}$  5.86 and 8.43  $\mu$ .

**1,1'-Carbonylbis-4-methylpiperazine Dihydrochloride (77).**—The following procedure is a simplified version of the process of Kushner, *et al.*<sup>18</sup> To a well-stirred solution of 80.1 g (0.8 mole) of 1-methylpiperazine in 300 ml of CH<sub>2</sub>Cl<sub>2</sub> kept at <–30° with a Dry Ice–MeOH bath was added in a thin stream 200 ml of a cold (5°) 2 M solution of COCl<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub>. Cooling was then stopped. After 2 hr the resulting solid was collected, washed with EtOH, then dried at 90° and ca. 1 mm; 82.6 g (70%), mp 304–305° dec (lit.<sup>18</sup> mp 303–304°).

**1,1'-Oxalylbis-4-methylpiperazine (84).**—Diethyl oxalate (18 ml, 19.5 g, 133 mmoles) and 40 ml (0.4 mole) of N-methylpiperazine were mixed and heated on a steam bath for 7 hr. The excess N-methylpiperazine was evaporated and the resulting syrup was dissolved in 25 ml of ether. The product crystallized

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quickly; yield 18.0 g. This was recrystallized from 1 l. of heptane; yield 14.8 g.

**N-[2-(4-Methyl-1-piperazinylsulfonyl)ethyl]phthalimide (XIX).**—N-Methylpiperazine (10 g, 0.10 mole) in 250 ml of toluene was added to a slurry of 27.5 g (0.10 mole) of 2-phthalimidoethanesulfonyl chloride<sup>19</sup> in 250 ml of toluene over a 50-min period. The reaction mixture was stirred for an additional 2.0 hr then filtered; yield 30.4 g (81%), mp 249–259° dec. This product was dissolved in a boiling solution of 330 ml of 95% EtOH containing 50 ml of H<sub>2</sub>O, treated with Darco, and filtered. Five milliliters of concentrated HCl was added to the filtrate which was chilled and filtered to afford 24 g (64% yield) of product, mp 263–270° dec. *Anal.* (C<sub>15</sub>H<sub>20</sub>ClN<sub>3</sub>O<sub>4</sub>S) C, H, N, S.

Crude sulfonamide (35 g) was dissolved in 450 ml of warm H<sub>2</sub>O, treated with Darco, and filtered. NaOAc (30 g) was added to the filtrate which was chilled and filtered; yield 14.4 g (45%), mp 172.5–175°. For analyses a small portion of this product was recrystallized from EtOAc–EtOH (3:1), mp 172–175.5°. *Anal.* (C<sub>15</sub>H<sub>19</sub>N<sub>3</sub>O<sub>4</sub>S) C, H, N, S.

**1-(2-Dimethylaminoethylsulfonyl)-4-methylpiperazine Dihydrochloride (85).**—A mixture of 14.25 g (0.042 mole) of XIX, 2.06 ml (0.042 mole) of NH<sub>2</sub>NH<sub>2</sub>·H<sub>2</sub>O, 100 ml of EtOH, and 10 ml of H<sub>2</sub>O was refluxed for 3.5 hr then evaporated to dryness. The residue was slurried in 100 ml of hot H<sub>2</sub>O, brought to pH 1 by adding concentrated HCl, chilled, and filtered to remove the phthalhydrazide. The filtrate was evaporated to a viscous oil and a solution of 50 ml of 37% formaldehyde and 50 ml of 97% HCOOH was added. After having been heated for 20 hr on a steam bath the reaction mixture was evaporated to an oily liquid *in vacuo*, dissolved in 100 ml of H<sub>2</sub>O, and again evaporated. This latter procedure was repeated twice and the second time 5.0 ml of concentrated HCl was added. The resulting oil was crystallized from 100 ml of EtOH; yield 5.1 g, mp 214–217° dec. Concentration of the filtrate afforded 3.9 g, mp 214–216° dec. The two crops were combined and recrystallized from a solution of 50 ml of EtOH and 5 ml of H<sub>2</sub>O containing 1.0 ml of concentrated HCl; yield 6.0 g, mp 215–217.5° dec. The addition of ether to the filtrate gave more crystals; yield 1.5 g (58%), mp 213–216° dec. *Anal.* (C<sub>8</sub>H<sub>22</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>2</sub>S) C, H, Cl, N, S.

**N,N-Bis(2-diethylaminoethyl)-4-methylpiperazine-1-carboxamide (87).**—4-Methylpiperazine-1-carbonyl chloride hydrochloride<sup>5</sup> (16 g, 0.08 mole) was added to 25 ml of cold H<sub>2</sub>O, covered with 100 ml of C<sub>6</sub>H<sub>6</sub>, and saturated with anhydrous K<sub>2</sub>CO<sub>3</sub> in an ice bath. The mixture was shaken vigorously and the C<sub>6</sub>H<sub>6</sub> layer was decanted. The slurry was extracted with an additional three 100-ml and two 50-ml portions of C<sub>6</sub>H<sub>6</sub> which were combined and dried (MgSO<sub>4</sub>). The C<sub>6</sub>H<sub>6</sub> was removed and the resulting crystalline solid was dissolved in 75 ml of toluene and cooled in an ice bath. Bis(2-diethylaminoethyl)amine (14.5 g, 0.067 mole) dissolved in 50 ml of toluene was added over a 40-min period with stirring. The reaction mixture was stirred at room temperature for 0.5 hr then refluxed for 1.0 hr. After having been cooled to room temperature the mixture was diluted with 50 ml of toluene and filtered from a crystalline solid. The ir spectrum of this material showed no absorption in the C=O region, hence it was discarded. The filtrate from this product was evaporated at reduced pressure and the resulting oil dissolved in petroleum ether. This solution deposited 2.8 g of 1,1'-carbonylbis-4-methylpiperazine on cooling. The crystals were collected and discarded. The filtrate was evaporated and the residue distilled; yield 8.1 g, bp 146–148° (0.075 mm), *n*<sub>D</sub><sup>20</sup> 1.4813. *Anal.* (C<sub>18</sub>H<sub>30</sub>N<sub>3</sub>O) C, H, N.

**N,N'-Dimethyl-N,N'-bis(2-dimethylaminoethyl)sulfamide (90).**—N,N,N'-Trimethylenediamine (30.6 g, 0.30 mole) was dissolved in 75 ml of CHCl<sub>3</sub> and chilled in an ice bath. To this solution was added a solution of SO<sub>2</sub>Cl<sub>2</sub> (7.5 ml, 0.09 mole) dissolved in 30 ml of CHCl<sub>3</sub> over a 40-min period with stirring. After having been stirred for an additional 1 hr at room temperature the solvent was removed by evaporation and the residue was dissolved in 50 ml of 5 N NaOH. The solution was extracted with 100 ml of ether, 10 ml of 10 N NaOH was added and again extracted with 100 ml of ether. The latter procedure was repeated and the combined ether extracts were dried (MgSO<sub>4</sub>). The ether was evaporated at reduced pressure and the residue distilled; yield 4.4 g, bp 113–115° (0.03 mm), *n*<sub>D</sub><sup>20</sup> 1.4637. *Anal.* (C<sub>10</sub>H<sub>16</sub>N<sub>4</sub>O<sub>2</sub>S) C, H, N, S.

**Bis(2-Diethylaminoethyl) Methylphosphonate Dihydrochloride (91).**—To a well-stirred, cooled (0–10°) solution of 17.5 g (0.15 mole) of 2-diethylaminoethanol in 50 ml of CHCl<sub>3</sub> was added over a period of 1 hr 9.9 g (0.075 mole) of methylphosphonic dichloride dissolved in 25 ml of CHCl<sub>3</sub>. The reaction mixture was stirred for 17 hr at room temperature. Evaporation of the solvent gave a solid; yield 24.0 g. This was dissolved in 150 ml of hot EtOH, and ether (180 ml) was added to incipient turbidity. This was cooled to give a solid, yield 15.8 g (58%), mp 154–156°. *Anal.* (C<sub>14</sub>H<sub>24</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>3</sub>P) C, H, Cl, N.

**Tris(2-diethylaminoethyl) Phosphate Trihydrochloride (92).**—To a well-cooled (0–10°), stirred solution of 11.7 g (0.10 mole) of 2-diethylaminoethanol in 50 ml of CHCl<sub>3</sub> was added dropwise a solution of 5.1 g (0.033 mole) of POCl<sub>3</sub> in 25 ml of CHCl<sub>3</sub>. The mixture was heated to reflux for 16 hr and cooled, and the product was collected; yield 7.8 g, mp 189–190°. This was recrystallized from 100 ml of EtOH; yield 4.8 g (28%), mp 198–199°. *Anal.* (C<sub>18</sub>H<sub>36</sub>Cl<sub>3</sub>N<sub>3</sub>O<sub>4</sub>P) C, H, Cl, N.

**N-Ethyl-N-(2-hydroxyethyl)trifluoroacetamide (XX).**—Ethyl trifluoroacetate (100 g) was added over 1.5 hr with stirring to N-ethylaminoethanol (400 ml). The excess amino alcohol was removed on a water bath at 10 mm to afford 151 g of product, *n*<sub>D</sub><sup>20</sup> 1.4154. Crude product (50 g) was purified by distillation; yield 35.8 g, bp 58–62° (0.10 mm), *n*<sub>D</sub><sup>20</sup> 1.4085. *Anal.* (C<sub>6</sub>H<sub>10</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>) H, F, N; C: calcd, 39.0; found, 39.7.

**N-Trifluoroethyl-N-ethylaminoethanol (XXI).**—To a stirred solution of 1.0 M borane (1.0 l.) in an ice bath was added during 1.5 hr 100 g (0.585 mole) of N-ethyl-N-(2-hydroxyethyl)trifluoroacetamide (XX) dissolved in 200 ml of dry THF under N<sub>2</sub>. The mixture was refluxed for 1.0 hr, cooled, stirred, and treated with a solution of 90 ml of THF containing 10 ml of H<sub>2</sub>O, followed by 100 ml of 6 N HCl. The solid was removed by filtration and the filtrate was evaporated to dryness. The residue was diluted with 100 ml of H<sub>2</sub>O, made strongly basic by adding solid NaOH, and extracted with four 150-ml aliquots of ether. The combined ether extracts were dried (MgSO<sub>4</sub>) and evaporated, and the residue distilled; yield 43.4 g (43%), bp 162–166°, *n*<sub>D</sub><sup>20</sup> 1.3843. This material was satisfactory for the preparation of 27 and 93.

**2-(N-Trifluoroethyl-N-ethylamino)ethyl 4-Trifluoroethylpiperazine-1-carboxylate (93).**—Ethyl 4-trifluoroethylpiperazine-1-carboxylate<sup>20</sup> (12.0 g, 0.05 mole), N-trifluoroethyl-N-ethylaminoethanol (26.2 g, 0.15 mole) (XXI), and NaOMe (0.5 g) were heated in a spinning band distillation apparatus for 3.0 hr at 80° (12 mm) followed by 3.0 hr at 90° (12 mm) and finally 2.0 hr at 105° (12 mm). The reaction mixture was then distilled and the fraction boiling at 101–102° (0.1 mm) was collected; yield 13.7 g (75%), *n*<sub>D</sub><sup>20</sup> 1.4187. *Anal.* (C<sub>15</sub>H<sub>22</sub>F<sub>6</sub>N<sub>4</sub>O<sub>2</sub>) H, N, F; C: calcd, 42.7; found, 43.5.

**Dimethochloride of 2-Diethylaminoethyl 4-Methylpiperazine-1-carboxylate (94).**—2-Diethylaminoethyl 4-methylpiperazine-1-carboxylate (9.6 g, 40 mmoles) was dissolved in 200 ml of warm EtOH and treated with 10 ml (22.6 g, 160 mmoles) of CHCl<sub>3</sub>. This was warmed to a gentle reflux for 30 min, allowed to stand at room temperature for 3 hr and then cooled overnight; yield of crystalline product 20.7 g (98%), mp 249–252° dec. For analyses a 2.0-g sample was recrystallized from 120 ml of EtOH; yield 1.7 g, mp 249–252° dec (temperature raised at 4°/min). *Anal.* (C<sub>14</sub>H<sub>22</sub>I<sub>2</sub>N<sub>4</sub>O<sub>2</sub>) C, H, N; I: calcd, 48.2; found, 47.4.

A mixture of 8.4 g (16 mmoles) of the dimethiodide, 60 g of the ion-exchange resin, Dowex Ag 1-XS (chloride form), and 180 ml of H<sub>2</sub>O was stirred for 2.5 hr and filtered. The filtrate was evaporated to a small volume and then coevaporated several times with EtOH to give a solid residue. This was dissolved in 20 ml of warm EtOH, filtered, and cooled and ether was added very slowly to give a crystalline product. This was cooled overnight and the product was collected; yield 4.5 g (86%), mp 243–247°. Recrystallization from EtOH–EtOAc yielded 3.8 g, mp 249–251° dec. *Anal.* (C<sub>14</sub>H<sub>20</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>2</sub>·H<sub>2</sub>O) C, H, Cl, N.

**2-Diethylaminoethyl 4-Methylpiperazine-1-carboxylate N,4-Dioxide (95).**—A solution of 10.0 g (43.0 mmoles) of 2-diethylaminoethyl 4-methylpiperazine-1-carboxylate and 12 ml (104 mmoles) of 30% H<sub>2</sub>O<sub>2</sub> in 40 ml of EtOH was allowed to stand at room temperature for 40 hr. The solution was evaporated to a syrup which was coevaporated several times with EtOH. The viscous syrup was dissolved in a little EtOH and excess ether was added to precipitate the syrup. The solvent was

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decanted and the procedure was repeated. (This was to separate starting material which is soluble in ether.) The residue was evacuated over  $P_2O_5$  to give a solid glass which was dissolved in EtOH and saturated with HCl. This was evaporated to a syrup which was dissolved in 6 ml of EtOH to give 11 ml of solution, which was seeded with material prepared previously by a similar process. After the mixture had been cooled overnight the product was collected (yield 4.2 g) and recrystallized from 10 ml of EtOH; yield 3.4 g (23%), mp 143–148°,  $\lambda_{\max}^{N_{10}O_1}$  3.95 and 5.83  $\mu$ . *Anal.* ( $C_{12}H_{27}Cl_2N_3O_4$ ) C, H, Cl, N.

**trans-2-Dimethylaminocyclopentanol (XXII).**—Cyclopentane oxide (9.6 g, 0.114 mole) was added to a solution of 50 ml of  $H_2O$  previously saturated with anhydrous  $Me_2NH$  in an ice bath. The reaction mixture was stoppered and allowed to stand at room temperature for 5 days. The  $H_2O$  and excess  $Me_2NH$  were removed at reduced pressure on a water bath and the residue was distilled; yield 11.2 g (76%), bp 95–96° (10 mm),  $n_D^{25}$  1.4727 (lit.<sup>21</sup> bp 94–95° (11 mm),  $n_D^{25}$  1.4710). *Anal.* ( $C_7H_{15}NO$ ) N.

**(±)-erythro-1-Phenyl-2-dimethylaminoopropanol (XXIII).**—(±)-erythro-1-Phenyl-2-aminopropanol hydrochloride (mp 194–197°) (18.8 g, 0.10 mole), 12 ml of  $H_2O$ , 85 ml of 97%  $HCOOH$ , and 85 ml of 37% formaldehyde were mixed and heated on a steam bath for 19 hr. The reaction mixture was evaporated to dryness at reduced pressure, dissolved in 75 ml of  $H_2O$ , and again evaporated. This latter procedure was repeated twice more and the resulting crystalline residue was recrystallized from 50 ml of 95% EtOH; yield 4.7 g, mp 207–209°. Additional materials, 4.95 g, mp 204–206.5°, and 6.25 g, mp 204–207°, were obtained from the filtrate (74% total yield). *Anal.* ( $C_{11}H_{18}ClNO$ ) C, H, Cl, N. This hydrochloride (13.0 g, 0.06 mole) was dissolved in 25 ml of  $H_2O$  and 15 ml of 10 *N* NaOH was added. The mixture was extracted with three 100-ml portions of ether which were combined and dried ( $MgSO_4$ ). Evaporation of the ether gave a white crystalline solid; yield 10.6 g, mp 60.5–65°. A small portion of this compound was recrystallized from petroleum ether; mp 65–67.5°.

**Bis(2-diethylaminoethyl) 4,4'-Ethylene-di(1-piperazinecarboxylate) (96).**—A solvent was included in this experiment to prevent premature precipitation of a monoalkylation product. A solution of 9.37 g (0.05 mole) of  $BrCH_2CH_2Br$  and 22.93 g (0.1 mole) of 2-diethylaminoethyl piperazine-1-carboxylate (2) in 100 ml of EtOH was heated under reflux for 15 hr. A little solid had separated. The mixture was evaporated to dryness and the residue dissolved in 20 ml of hot  $H_2O$ . This solution

was chilled during the portionwise addition with shaking of 11.22 g (0.2 mole) of KOH. The resulting slush was extracted by decantation with 100 ml, then three 20-ml portions of ether. The ethereal extracts were dried ( $K_2CO_3$ ), filtered, then evaporated. The residual oil was distilled *in vacuo* without a fractionating column, using a Claisen distillation head leading directly to a vacuum adapter connected to the receiver. The adapter alone provided ample condensing surface. An oil bath heated with a hot plate gave only enough heat for removal of a forerun. Much more effective heating was provided by an "air bath chimney" made from two layers of aluminum foil formed into a cylinder and suspended from a metal ring. A wire gauze with a center circle of asbestos hung from three wires which held it near the bottom of the chimney. The gauze was heated with a wide, soft flame from a Meker burner. The still pot was not clamped in place. Instead, the pot, Claisen head, adapter, and receiver (all with 24/40  $\frac{1}{2}$  glass joints) were wired together. Thus all of the pot and part of the Claisen head could be heated in the chimney. The whole assembly balanced nicely, the side arm of the Claisen head resting on the foil-covered iron ring. An ebullator was unnecessary; the pot charge was readily kept swirling by gently rocking the whole assembly of glassware. There was no sign of charring or decomposition in the pot. An intermediate cut amounted to 0.62 g, bp  $\sim 246^\circ$  (0.09 mm),  $n_D^{25}$  1.4946. Collection of the product was begun when the distillate no longer darkened as it ran down the adapter. The product was 16.2 g (67%) of a very viscous, light yellow oil which later crystallized completely; bp 250–255° (0.1 mm),  $n_D^{25}$  1.4942, mp 30–32°. *Anal.* ( $C_{24}H_{48}N_8O_4$ ) C, H, N.

**2-Diethylaminoethyl 2-Methoxyethyl Carbonate (100).**—A procedure used for the preparation of *n*-butyl chloroformate<sup>22</sup> was adapted for the synthesis of 2-methoxyethyl chloroformate; 96% yield, bp 70° (30 mm),  $n_D^{26.6}$  1.4161 (lit.<sup>23</sup> bp 59° (13 mm),  $n_D^{25}$  1.4163). A solution of 17.60 g of 2-diethylaminoethanol in 75 ml of  $CH_2Cl_2$  was gradually added to a cold solution of 20.80 g of 2-methoxyethyl chloroformate in 150 ml of  $CH_2Cl_2$ . After 5 days at about 26° the mixture was worked up as described in procedure C, except that the basification was with 20.0 g of anhydrous  $K_2CO_3$ . Two successive fractionations gave 14.78 g (45%) of product, bp 72° (0.06 mm),  $n_D^{26.7}$  1.4319,  $\lambda_{\max}^{neat}$  5.73 and 7.85  $\mu$ . *Anal.* ( $C_{10}H_{21}NO_4$ ) C, H, N.

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## Structural Aspects of Picrotoxinin Action

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A number of compounds related to picrotoxinin have been tested for ability to mimic the action of that compound. Active compounds have a free bridgehead hydroxyl group and a lactone ring connecting carbons 3 and 5 of the picrotoxane (I) skeleton. The axial isopropenyl substituent group of picrotoxinin appears to have a role in determining potency.

Picrotoxin, recently reviewed by one of us,<sup>1</sup> is an ancient<sup>2–4</sup> drug component of *Anamirta paniculata* and *cocculus*. It is an efficient analeptic,<sup>5</sup> but seldom used. Despite its therapeutic obsolescence picrotoxin is of much theoretical interest because of its site and mode of action in the central nervous system. It appears to

competitively depress presynaptic inhibition in the vertebrate spinal cord and not to effect postsynaptic inhibitory processes.<sup>6</sup> The anatomical specificity in action prompted our interest. The generalization that only its picrotoxinin (II) component was active and that picrotin (III) was inactive was also of interest since their only difference is hydration of the isopropenyl group. In connecting this information it was thought that presynaptic inhibitory receptors should show high structure discrimination and that structure-activity re-

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