Analogs of Heterocyclic CNS Agents

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Thirty-five oxazoles, thiazoles, piperazines and related compounds, analogs of known CNS agents, were prepared and tested. None were more active than the lead compounds.

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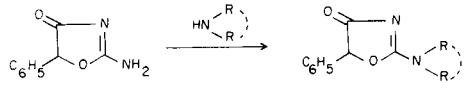
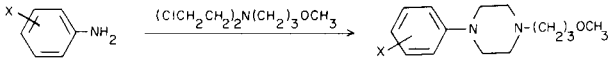
In our search for better drugs for the treatment of central nervous system diseases we have prepared a number of heterocyclic compounds analogous to known CNS agents. For example, compounds of type I are related to the CNS stimulant pemoline (2) and compounds of type II are analogs of the hypotensive and CNS depressants reported by A. H. Sommers (3).

In general the oxazolin-ones were prepared by exchanging the NH_2 group of pemoline with a higher boiling amine.



pemoline I

The piperazines were made by closing the ring by reacting a bis(chloroethyl)amine with a primary amine.



II.

These and some related oxazoles, thiazoles, and piperazines are listed in Chart I and their preparations are described in the Experimental. They were tested in mice in a battery of tests (4) designed to uncover CNS activities; however, none proved more useful than the lead compounds.

EXPERIMENTAL

2-(2-Methyl-1-pyrrolidinyl)-5-phenyl-2-oxazolin-4-one (**1**).

A mixture of 17.6 g. (0.1 mole) of 2-imino-5-phenyl-4-oxazolidinone (2) and 15 g. (0.18 mole) of 2-methylpyrrolidine in 500 ml. of ethanol was stirred under reflux overnight. Filtration and evaporation *in vacuo* gave a syrup which slowly crystallized. This was recrystallized from 2-propanol yielding 12.6 g. (52%) of white crystals, m.p. 137.5/139°. Ir and nmr support the structure.

2-(2,2-Dimethyl-1-pyrrolidinyl)-5-phenyl-2-oxazolin-4-one (**2**).

This compound was prepared by the procedure used for **1** from 17.6 g. (0.1 mole) of 2-imino-5-phenyl-4-oxazolidinone (2), 14.85 g. (0.15 mole) of 2,2-dimethylpyrrolidine (5) and 100 ml. of 2-methoxyethanol in place of the ethanol. After removal of the solvent *in vacuo* the residue was recrystallized from benzene-hexane yielding 17.5 g. (68%) of white solid, m.p. 88-91°. A sample recrystallized for analysis had m.p. 95-98°. Ir supports the structure.

2-Azaspiro[4,5]decan-1-yl-5-phenyl-2-oxazolin-4-one (**3**).

This compound was prepared by the procedure used for **1** from 17.6 g. (0.1 mole) of 2-imino-5-phenyl-4-oxazolidinone (2), 20.8 g. (0.15 mole) of 1-azaspiro[4,5]decane (6) and 100 ml. of 2-methoxyethanol. After removal of the solvent *in vacuo* the residue was recrystallized from 2-propanol yielding 21.5 g. (72%) of white crystals, m.p. 140.5-141.5°. Ir and nmr support the structure.

5-Phenyl-2-(thiomorpholino)-2-oxazoline-4-one (**4**).

This compound was prepared by the procedure used for **1** from 17.6 g. (0.1 mole) of 2-imino-5-phenyl-4-oxazolidinone (2), 15.5 g. (0.15 mole) of thiomorpholine and 100 ml. of 2-methoxyethanol. On cooling the reaction mixture deposited crystals which were recrystallized from 2-methoxyethanol yielding 17.8 g. (68%) of white crystals, m.p. 189.5-190.5°. Ir supports the structure.

2-Methyl-6,7-benzoxazolediol (**5**).

A solution of 5.13 g. (0.03 mole) of 4-nitropyrogallol (7) and 29.4 ml. (0.3 mole) of acetic anhydride in 70 ml. of acetic acid was warmed on a steam bath for 1 hour, cooled, and hydrogenated with 0.2 g. of platinum oxdie at 3.5 kg./cm^2 and room temperature. After filtration and evaporation, under nitrogen, the residue was heated at 245° for 1 hour. The product was dissolved in ethanol, treated with decolorizing charcoal and evaporated *in vacuo*. The residue crystallized slowly. Boiling with ethyl acetate and filtering gave solid which was recrystallized from ethanol yielding 1.8 g. of light brown solid, which ir and nmr showed to be a mixture of the 6 and 7 mono acetates of **5**.

Anal. Calcd. for $C_{10}H_9NO_4$: C, 57.97; H, 4.38; N, 6.76. Found: C, 57.82; H, 4.23; N, 6.81.

A solution of 0.45 g. of the above acetate in 20 ml. of methanol was adjusted to *p*H 9 with 10% aqueous sodium hydroxide and allowed to stand at room temperature for 2 hours. Neutralization with acetic acid, treatment with decolorizing charcoal, concentration, dilution with water, and cooling in the refrigerator yielded 0.25 g. of crystals. This product was recrystallized from water yielding 0.17 g. (14% overall) yield of nearly white crystals, m.p. 175-180°. A sample sublimed at 0.02 mm from a bath up to 200° gave white solid, m.p. 179-181°. Ir supports the structure.

2-(3,4,5-Trimethoxyphenyl)benzoxazole (**6**).

A mixture of 10.9 g. (0.1 mole) of *o*-aminophenol and 21.2 g. (0.1 mole) of 3,4,5-trimethoxybenzoic acid was heated, with stirring under nitrogen at 240° for 2.25 hours. The resulting gum was triturated with dilute aqueous sodium hydroxide and filtered. The insoluble brown solid was recrystallized from ethanol with the aid of decolorizing charcoal yielding 5.3 g.

0022-152X/80/040753-06$02.25

Chart I

Structures and Analyses

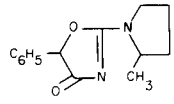
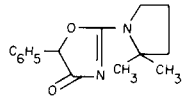
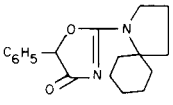
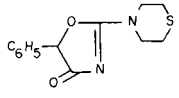
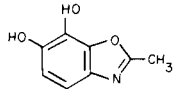
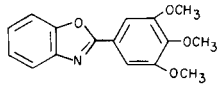
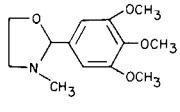
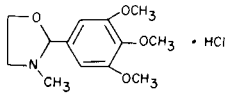
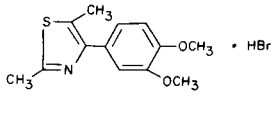
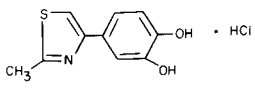
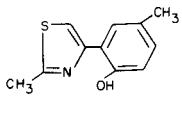
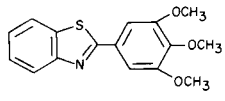
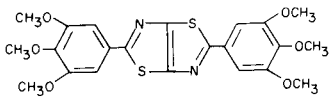
Compound No.	Structure	Molecular Formula	Analysis (a) C	H	N	Other
1		$C_{14}H_{16}N_2O_2$	68.79 (68.83)	6.49 (6.60)	11.49 (11.49)	
2		$C_{15}H_{18}N_2O_2$	69.44 (69.74)	7.12 (7.02)	11.11 (10.85)	
3		$C_{18}H_{22}N_2O_2$	72.37 (72.45)	7.37 (7.43)	9.46 (9.39)	
4		$C_{13}H_{14}N_2OS$	59.52 (59.52)	5.27 (5.38)	10.48 (10.68)	S, 12.10 (12.22)
5		$C_8H_7NO_3$	57.99 (58.18)	4.44 (4.27)	8.60 (8.48)	
6		$C_{16}H_{15}NO_4$	67.52 (67.36)	5.56 (5.30)	5.12 (4.91)	
7		$C_{13}H_{19}NO_4$	61.99 (61.64)	7.53 (7.56)	5.39 (5.53)	
8		$C_{13}H_{20}ClNO_4$	53.14 (b) (53.88)	7.17 (6.96)	5.11 (4.83)	S, 12.66 (12.24)
9		$C_{13}H_{16}BrNO_2S$	47.06 (47.28)	4.89 (4.88)	4.03 (4.24)	S, 10.02 (9.71) (c)
10		$C_{10}H_{10}ClNO_2S$	49.39 (49.28)	4.34 (4.14)	5.35 (5.75)	S, 13.09 (13.16) (d)
11		$C_{11}H_{12}ClNOS$	54.98 (54.65)	4.89 (5.00)	–	S, 13.45 (13.26) (e)
12		$C_{16}H_{15}NO_3S$	63.45 (63.76)	4.94 (5.02)	4.48 (4.65)	
13		$C_{22}H_{22}N_2O_6S_2$	55.37 (55.68)	4.67 (4.67)	5.81 (5.90)	S, 13.48 (13.51)

Chart I – Continued

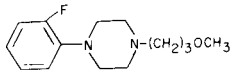
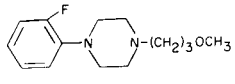
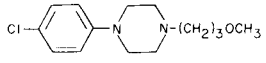
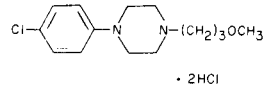
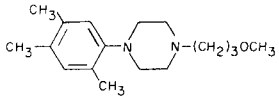
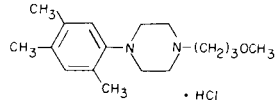
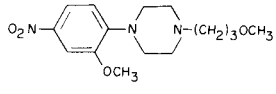
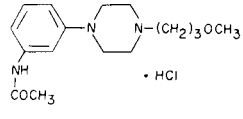
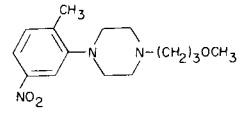
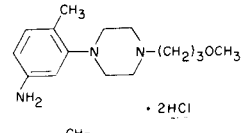
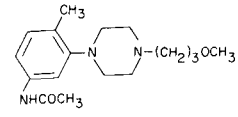
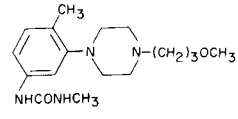
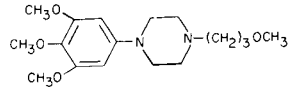
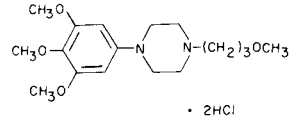
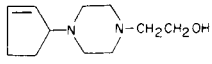
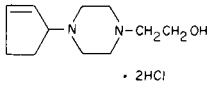
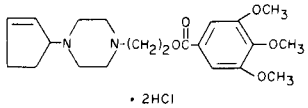
Compound No.	Structure	Molecular Formula	Analysis (a) C	H	N	Other
16		$C_{14}H_{21}FN_2O$	66.63 (66.70)	8.64 (8.33)	10.79 (11.11)	F, 6.93 (7.53)
17		$C_{14}H_{22}ClFN_2O$	58.33 (58.22)	7.86 (7.63)	9.56 (9.70)	F, 6.26 (6.39) (f)
19		$C_{14}H_{21}ClN_2O$	62.32 (62.68)	7.80 (7.83)	10.33 (10.44)	Cl, 13.36 (13.05)
20		$C_{14}H_{23}Cl_3N_2O$	49.31 (49.26)	6.39 (6.74)	–	Cl, 31.05 (31.08)
21		$C_{17}H_{28}N_2O$	73.94 (73.91)	10.42 (10.14)	10.42 (10.14)	
22		$C_{17}H_{29}ClN_2O$	65.03 (65.25)	9.08 (9.34)	8.93 (8.95)	Cl, 11.35 (11.34)
23		$C_{15}H_{23}N_3O_4$	57.96 (58.25)	7.35 (7.44)	13.70 (13.59)	
25		$C_{16}H_{26}ClN_3O_2$	58.78 (58.60)	8.12 (7.93)	12.71 (12.82)	Cl, 10.90 (10.92)
27		$C_{15}H_{23}N_3O_3$	61.75 (61.41)	8.02 (7.90)	14.64 (14.32)	
28		$C_{15}H_{27}Cl_2N_3O$	53.69 (53.57)	8.04 (8.05)	12.64 (12.50)	Cl, 21.26 (21.10)
29		$C_{17}H_{27}N_3O_2$	66.97 (66.91)	8.97 (8.85)	13.91 (13.77)	
30		$C_{17}H_{28}N_4O_2$	63.69 (63.75)	8.44 (8.75)	17.55 (17.50)	
31		$C_{17}H_{28}N_2O_4$	62.74 (62.94)	8.79 (8.70)	8.36 (8.63)	
32		$C_{17}H_{30}Cl_2N_2O_4$	51.53 (51.38)	7.59 (7.61)	7.24 (7.05)	Cl, 17.69 (17.85)

Chart I – Continued

Compound No.	Structure	Molecular Formula	Analysis (a) C	H	N	Other
33		$C_{11}H_{20}N_2O$	67.11 (67.30)	10.28 (10.27)	14.24 (14.28)	
34	 · 2HCl	$C_{11}H_{22}Cl_2N_2O$	48.97 (49.07)	8.30 (8.24)	–	Cl, 26.27 (26.34)
35	 · 2HCl	$C_{21}H_{32}Cl_2N_2O_5$	54.52 (54.43)	6.92 (6.96)	6.29 (6.05)	Cl, 15.32 (15.30)

(a) Values in parentheses are calculated. (b) This hydrochloride proved to be very hydroscopic and difficult to analyze, which probably explains the poor carbon analysis. (c) Calcd.: Br, 24.20. Found: Br, 25.01. (d) Calcd.: Cl, 14.55. Found: Cl, 14.20. (e) Calcd.: Cl, 14.67. Found: Cl, 14.71. (f) Calcd.: Cl, 12.29. Found: Cl, .2.26.

(19%) of nearly white crystals, m.p. 113-115.5°. Ir supports the structure.

3-Methyl-2-(3,4,5-trimethoxyphenyl)oxazolidine (**7**).

A solution of 39.2 g. (0.2 mole) of 3,4,5-trimethoxybenzaldehyde and 15.8 g. (0.21 mole) of 2-(methylamino)ethanol in 100 ml. of benzene was refluxed for 0.5 hour with a water separator. After removal of the solvent *in vacuo* the product was distilled yielding 42.0 g. (83%) of nearly colorless liquid, b.p. 127°/0.04 mm, n_D^{25} 1.5364.

Hydrochloride (**8**).

A solution of 2.5 g. (0.01 mole) of this free base (**7**) in 40 ml. of absolute ether was acidified with ethanolic hydrogen chloride. The resulting solid was collected, washed with ether and dried yielding 2.65 g. (91%) of white solid, m.p. 163-167°. Ir supports the structure which hydrolyzes very rapidly in water.

4-(3,4-Dimethoxyphenyl)-2,5-dimethylthiazole Hydrobromide (**9**).

A solution of 27.3 g. (0.1 mole) of 2-bromo-3′,4′-dimethoxypropiophenone and 8.3 g. (0.11 mole) of thioacetamide in 50 ml. of ethanol was refluxed for 4 hours. Concentration and cooling yielded 9.0 g. (27%) of white solid, m.p. 202-205°. A sample for analysis was recrystallized from ethanol, m.p. 202-205.5°. Ir supports the structure.

4-(3,4-Dihydroxyphenyl)-2-methylthiazole Hydrochloride (**10**).

A mixture of 37.3 g. (0.2 mole) of 2-chloro-3′,4′-dihydroxyacetophenone and 15.03 g. (0.2 mole) of thioacetamide in 100 ml. of ethanol was refluxed for 0.5 hour. After standing, under nitrogen, at room temperature for 3 days the solid was collected and washed with ethanol giving 42.6 g. (88%) of gray solid, m.p. 248-255° dec. Recrystallization from methanol-2-propanol with the aid of decolorizing charcoal yielded 35 g. of white crystals, m.p. 250-260° dec. Ir and uv support the structure.

2-Methyl-4-(2-hydroxy-5-methylphenyl)thiazole Hydrochloride (**11**).

A solution of 18.5 g. (0.1 mole) of 2-chloro-2′-hydroxy-5′-methyl-acetophenone (8) and 8.27 g. (0.11 mole) of thioacetamide in 100 ml. of ethanol was refluxed for 1 hour and allowed to stand overnight. Filtration, evaporation, and recrystallization from ethanol yielded 17 g. (71%) of white crystals, m.p. 225-227° dec. Ir and uv support the structure.

2-(3,4,5-Trimethoxyphenyl)benzthiazole (**12**).

A mixture of 25 g. (0.2 mole) of *o*-aminophenol and 42.4 g. (0.2 mole) of 3,4,5-trimethoxybenzoic acid was stirred under nitrogen at 250° for 8 hours. The resulting gum was dissolved in 300 ml. of ethanol, filtered, diluted with water and basified with sodium hydroxide. The solid was collected, washed with water, ethanol, dried, and recrystallized from ethanol yielding 14.4 g. (24%) of white crystals, m.p. 150.5-152°. Ir supports the structure.

2,5-[Di-(3,4,5-trimethoxyphenyl)]thiazolo[5,4-*d*]thiazole (**13**).

A mixture of 39.2 g. (0.2 mole) of 3,4,5-trimethoxybenzaldehyde, 4.9 g. (0.041 mole) of dithiooxamide, and 14.6 g. (0.155 mole) of phenol was heated under reflux with a water trap for 10 minutes. While still hot 120 ml. of ethanol was added and after cooling the product was collected, washed with ethanol, ether, dried, and recrystallized from dimethylformamide yielding 4.0 g. of yellow crystals, m.p. 258-259°. The structure is deduced by analogy with similar compounds prepared by Johnson and Ketcham (9) and is supported by ir.

2,2′-[(3-Methoxypropyl)imino]diethanol (**14**).

A mixture of 44.6 g. (0.5 mole) of 3-methoxypropylamine and 60 ml. (1.2 moles) of cold ethylene oxide was heated in an autoclave at 100° for 17.5 hours. The product was distilled through an efficient column yielding 79 g. (88%) of light yellow liquid, b.p. 125°/1.5 mm, n_D^{25} 1.4648. Ir and nmr support the structure.

Anal. Calcd. for $C_8H_{19}NO_3$: C, 54.21; H, 10.80; N, 7.90. Found: C, 54.10; H, 10.44; N, 7.71.

N,N-Bis(2-chloroethyl)-3-methoxypropylamine Hydrochloride (**15**).

A solution of 180 g. (1.0 mole) of **14** in 1 l. of benzene and 200 ml. of ether was converted to its hydrochloride by passing in hydrogen chloride gas. Then 1 l. of thionyl chloride was slowly added with stirring at 0°. The mixture was allowed to warm to room temperature, and after stirring overnight, it was stirred under reflux until evolution of sulfur dioxide and hydrogen chloride ceased (about 3 hours). The solution was evaporated *in vacuo*, diluted with ethanol and again evaporated yielding 252 g. (98%) of light brown oil sufficiently pure for the following preparations. A sample of this oil in 2-propanol was diluted with ether and on standing deposited light tan crystals. Re-

crystallization from ethyl acetate, with the aid of decolorizing charcoal yielded white crystals, m.p. 58.5-61.5°; reported by Sacconi and Morassi (10), prepared by a different method, m.p. 48-50°. Ir and nmr support the structure.

1-(*o*-Fluorophenyl)-4-(3-methoxypropyl)piperazine (**16**).

A solution of 104 g. (0.4 mole) of **15**, 49 g. (0.44 mole) of *o*-fluoroaniline and 180.4 g. (1.4 moles) of diisopropylethylamine in 300 ml. of ethanol was stirred under reflux for 5.5 hours. In order to remove unreacted primary and secondary amines, the solution was evaporated *in vacuo* and mixed with 300 ml. of 10% aqueous sodium hydroxide and 300 ml. of tetrahydrofuran. To this 64 ml. (0.5 mole) of benzenesulfonyl chloride was slowly added with stirring followed by 150 ml. more 10% sodium hydroxide. After refluxing for 15 minutes and concentrating *in vacuo* the mixture was diluted with ice water, made strongly alkaline with more sodium hydroxide, and extracted with ether. The ether solution was washed with dilute sodium hydroxide, water, and then extracted with dilute hydrochloric acid. After washing with water the ether was evaporated giving a white solid. This was recrystallized from 2-propanol yielding 28 g. (16%) of white needles, m.p. 121-123°. This was found by ir, ms and analysis to be *N*-(*o*-fluorophenyl)dibenzenesulfonamide **18**, but in view of the high nitrogen analysis it may not be very pure.

Anal. Calcd. for $C_{18}H_{14}FNO_4S_2$: C, 55.23; H, 3.60; F, 4.85; N, 3.58. Found: C, 55.22; H, 3.49; F, 5.03; N, 4.49.

The above aqueous acid solution was basified with sodium hydroxide and extracted with ether. The extract was washed with water, saturated sodium chloride solution, and dried over sodium sulfate. Filtration and evaporation gave a brown oil, which was distilled *in vacuo* yielding 20.6 g. (20%) of yellow liquid **16**, b.p. 121°/0.05 mm. Ir and nmr support the structure.

Hydrochloride (**17**).

A solution of 5.4 g. (0.02 mole) of this free base in ethanol was acidified with 0.02 mole of ethanolic hydrogen chloride. The resulting solid was dissolved by warming and on cooling 4.5 g. (73%) of white crystalline monohydrochloride **17** separated, m.p. 143-145°.

1-(*p*-Chlorophenyl)-4-(3-methoxypropyl)piperazine (**19**).

This compound was prepared by the procedure used for **16** from 32.2 g. (0.12 mole) of **15**, 19.5 g. (0.15 mole) of *p*-chloroaniline, and 77.4 g. (0.6 mole) of diisopropylethylamine, 175 ml. of ethanol, 30 ml. (0.18 mole) of benzenesulfonyl chloride and 100 ml. of 10% aqueous sodium hydroxide. The sulfonamide fraction was not worked up. The ether solution of the tertiary amine fraction was evaporated and the residue was distilled yielding 12.6 g. of yellow liquid, b.p. 191°/3 mm. This solidified and was recrystallized from 2-propanol yielding 7.5 g. (22%) of white crystals, m.p. 71-72°. Ir and nmr support the structure.

Dihydrochloride (**20**).

A solution of 7 g. (0.026 mole) of **19** in 2-propanol was acidified with an excess of ethanolic hydrogen chloride. The mixture was warmed to dissolve the solid and cooled yielding 8.9 g. (100%) of white crystals, m.p. 185-190° dec. Ir supports the structure.

1-(3-Methoxypropyl)-4-(2,4,5-trimethylphenyl)piperazine (**21**).

This compound was prepared by the procedure used for **19** from 52 g. (0.2 mole) of **15**, 32 g. (0.22 mole) of 2,4,5-trimethylaniline, 90.4 g. (0.7 mole) of diisopropylethylamine, 200 ml. of ethanol, 32 ml. (0.25 mole) of benzenesulfonyl chloride and 300 ml. of 10% aqueous sodium hydroxide. The free base was distilled, yielding 15.7 g. (28%) of yellow oil, b.p. 165°/1.5 mm. Ir and nmr support the structure.

Monohydrochloride (**22**).

An ethanolic solution of 9.0 g. (0.033 mole) of **21** was acidified with 3.66 ml. (0.033 mole) of 9.1*N* ethanolic hydrogen chloride. The resulting solid was dissolved by warming and on cooling gave 8.0 g. (80%) of white crystals, m.p. 249-251° dec.

1-(2-Methoxy-4-nitrophenyl)-4-(3-methoxypropyl)piperazine (**23**) and 2-(4-Nitro-*o*-anisidino)ethanol (**24**).

A mixture of 100.8 g. (0.6 mole) of 4-nitro-*o*-anisidine, 30 ml. of acetic acid, 30 ml. of water, and 120 ml. of ethylene oxide in a sealed pressure tube was stirred at room temperature for 12 days. After evaporation and neutralization with sodium hydroxide the mixture was extracted with ether. The extract was washed with water, dried over magnesium sulfate and evaporated *in vacuo* giving 50 g. of orange oil. Extraction of this oil with dilute aqueous hydrochloric acid left red solid which was collected and recrystallized from benzene yielding 25 g. (17%) of red crystals, m.p. 86-87.5°. Ir, nmr and analysis showed this to be the mono addition product **24**.

Anal. Calcd. for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.66; N, 13.21. Found: C, 51.08; H, 5.86; N, 13.19.

The above aqueous acid extract was basified with sodium hydroxide and extracted with ether. Washing with water, drying over magnesium sulfate, filtering and evaporating gave 10 g. of crude oil, the nmr of which, showed this product to be mostly a mixture of the mono-(**24**) and di-ethanol derivatives of 4-nitro-*o*-anisidine.

This crude oil in 100 ml. of benzene and 40 ml. of tetrahydrofuran was treated with 36 ml. of thionyl chloride and stirred under reflux for 2 hours. Evaporation *in vacuo* gave crude *N*,*N*-bis(2-chloroethyl)-4-nitro-*o*-anisidine as a yellow oil.

This oil was mixed with 11.6 g. (0.13 mole) of 3-methoxypropylamine in 100 ml. of 95% ethanol and stirred under reflux for 24 hours. The solution was evaporated, mixed with dilute hydrochloric acid and extracted with ether. The aqueous acid solution was basified with sodium hydroxide and extracted with ether. Washing the extract with water, drying over magnesium sulfate and evaporating *in vacuo* gave yellow solid. This was recrystallized from 2-propanol yielding 3 g. (3% overall) of yellow crystals, m.p. 87-89°. Ir, nmr and ms support the structure **23**.

1-(*m*-Acetamidophenyl)-4-(3-methoxypropyl)piperazine Monohydrochloride (**25**).

This compound was prepared by the procedure used for **19** from 52 g. (0.2 mole) of **15**, 40 g. (0.22 mole) of *m*-aminoacetanilide, 90.4 g. (0.7 mole) of diisopropylethylamine, 200 ml. of ethanol, 32 ml. (0.25 mole) of benzenesulfonyl chloride and 300 ml. of 10% aqueous sodium hydroxide. The product was extracted with methylene chloride. The extract was washed with water, dried, filtered and evaporated *in vacuo*. The crude free base was converted to the monohydrochloride in 2-propanol by the addition of one equivalent of ethanolic hydrogen chloride, m.p. 228-230°. Ir and nmr support the structure.

N,*N*-Bis(2-chloroethyl)-5-nitro-*o*-toluidine (**26**) (**11**).

To a solution of 12.0 g. (0.05 mole) of 2,2′-(5-nitro-*o*-tolylimino)diethanol (**11**,**12**) in 100 ml. of benzene and 40 ml. of tetrahydrofuran was added, in a slow stream, with stirring 36.3 ml. (0.5 mole) of thionyl chloride. The mixture was stirred under reflux for 2 hours and allowed to stand at room temperature for 2 days. Concentration *in vacuo* gave a solid which was recrystallized from 2-propanol yielding 12.9 g. (93%) of yellow crystals,

m.p. 69-71°. Kristian, *et al.*, report m.p. 65-66°. Ir supports the structure.

Anal. Calcd. for $C_{11}H_{14}Cl_2N_2O_2$: C, 47.67; H, 5.09; Cl, 25.58; N, 10.11. Found: C, 47.59; H, 5.21; Cl, 25.10; N, 9.91.

1-(2-Methyl-5-nitrophenyl)-4-(3-methoxypropyl)piperazine (**27**).

A solution of 11.1 g. (0.04 mole) of **26** and 10.7 g. (0.12 mole) of 3-methoxypropylamine in 70 ml. of 95% ethanol was stirred under reflux for 20 hours. Evaporation *in vacuo* gave an oil which was dissolved in dilute hydrochloric acid and extracted with ether. The acidic aqueous solution was basified with sodium hydroxide and extracted with ether. The ether solution was washed with water, dried over magnesium sulfate, filtered and evaporated. The resulting solid was recrystallized from hexane yielding 9.4 g. (81%) of yellow crystals, m.p. 74-75°. Ir and nmr support the structure.

1-(5-Amino-*o*-tolyl)-4-(3-methoxypropyl)piperazine Dihydrochloride (**28**).

A solution of 8.8 g. (0.03 mole) of **27** in 250 ml. of ethanol was hydrogenated with 0.2 g. of platinum oxide at 3.5 kg./cm^2 and room temperature. Filtration and evaporation *in vacuo* gave the free base of **28** as a yellow oil.

This free base was dissolved in 2-propanol and acidified with an excess of ethanolic hydrogen chloride. The resulting solid was dissolved by warming and on cooling crystals separated, yielding 9.1 g. (83%) of tan crystals, m.p. 255-258° dec. Ir and nmr support the structure.

3′-[4-(3-Methoxypropyl)-1-piperazinyl]-*p*-acetotoluidide (**29**).

A solution of 7 g. (0.025 mole) of the free base of **28** in 3.75 g. (0.036 mole) of acetic anhydride and 10 ml. of acetic acid was heated on a steam bath for 1 hour and poured into ice water. The solution was basified with sodium hydroxide and extracted with ether. Evaporation of the ether extract gave white solid which was recrystallized from benzene yielding 5 g. (65%) of white crystals, m.p. 124-125°. Ir and nmr support the structure.

1-[3-[4-(3-Methoxypropyl)-1-piperazinyl]-*p*-tolyl]-3-methylurea (**30**).

To a cold solution of 16.5 g. (0.05 mole) of the free base of **28** in benzene was added 20 ml. of cold methylisocyanate. After standing overnight the resulting solid was collected and recrystallized from ethyl acetate, yielding 13 g. (85%) of white crystals, m.p. 135.5-137°. Ir and nmr support the structure.

1-(3,4,5-Trimethoxyphenyl)-4-(3-methoxypropyl)piperazine (**31**).

This was prepared by the procedure used for **19** from 52 g. (0.2 mole) of **15**, 40 g. (0.22 mole) of 3,4,5-trimethoxyaniline, 90.4 g. (0.7 mole) of diisopropylethylamine, 200 ml. of ethanol, 32 ml. (0.25 mole) of benzenesulfonyl chloride, and 300 ml. of 10% aqueous sodium hydroxide. The product was distilled *in vacuo* yielding 20.8 g. (32%) of yellow liquid, b.p. 170°/0.03 mm; n_D^{25} 1.5401. Ir and nmr support the structure.

Dihydrochloride (**32**).

This free base in 2-propanol was acidified with an excess of ethanolic hydrogen chloride, warmed to dissolve the solid and cooled giving 23.5 g. of solid, m.p. 194-198°. Recrystallization from ethanol yielded 21.2 g. (86.5%) of white crystals, m.p. 196-201.5°. Ir supports the structure.

4-[2-Cyclopenten-1-yl)-1-piperazinethanol (**33**).

A solution of 378 g. (2.88 moles) of *N*-hydroxyethylpiperazine in 1 l. of ethyl acetate was cooled to 15° and 296 g. (2.88 moles) of cold 3-chlorocyclopentene (**13**) was added with stirring during 15 minutes. After stirring at 0° for 2 hours and standing at room temperature for 3 days the mixture was diluted with ether and extracted with dilute hydrochloric acid. The acid extract was washed with ether, basified with sodium hydroxide, and the product was continuously extracted with ether for 22 hours. The ether extract was dried over potassium carbonate, filtered, and evaporated. The product was distilled through a 12 inch, helices packed, column yielding 256 g. (45%) of colorless liquid, b.p. 136°/4 mm n_D^{25} 1.5187. Ir supports the structure.

Dihydrochloride (**34**).

An ethereal solution of 22 g. (0.11 mole) of **33** was acidified with an excess of ethanolic hydrogen chloride giving white solid which was recrystallized from ethanol yielding 24 g. (87%) of white crystals, m.p. 192-194° dec. Ir supports the structure.

2-[4-[2-Cyclopentenyl)-1-piperazenyl]ethyl 3,4,5-Trimethoxybenzoate Dihydrochloride (**35**).

A mixture of 11.7 g. (0.06 mole) of **34**, 13.8 g. (0.06 mole) of 3,4,5-trimethoxybenzoyl chloride, and 200 ml. of benzene was stirred under reflux for 2 hours, cooled, and extracted with dilute hydrochloric acid. The aqueous extract was basified with cold dilute sodium hydroxide and extracted with ether. The ether extract was washed with water, dried over sodium sulfate and filtered. This ether solution of the free base was converted to the dihydrochloride with an excess of ethanolic hydrogen chloride. The product was triturated with ethyl methyl ketone and ethyl acetate and recrystallized from 2-propanol yielding 17.8 g. (64%) of white solid, m.p. 207° dec. Ir supports the structure.

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