

Notes

1,4-Bis(2-indol-3-ylethyl)piperazines

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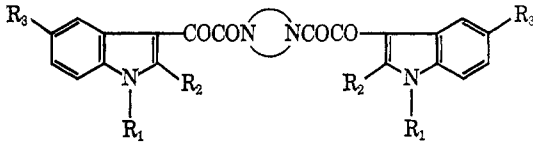



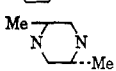
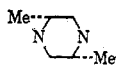


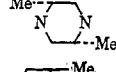
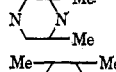
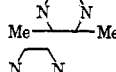
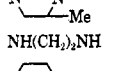
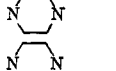


In a previous publication¹ we described a series of 1,4-bis(2-indol-3-ylethyl)piperidines possessing antihypertensive and central nervous system depressant activities. The pharmacological interest in that series prompted us to extend the work to include 1,4-bis(2-indol-3-ylethyl)piperazines and a considerable number of these compounds are described in our U. K. and U. S. Patents.^{2,3} A recent publication by Brewster, *et al.*,⁴ presented the synthesis of some 1,4-bis(2-indol-3-ylethyl)piperazines, two of which were disclosed in the foregoing patents; the remaining three differed in the position of a methoxyl substituent. The main pharmacological activity found by these authors was a long-lasting lowering of the blood pressure of meta-corticoid hypertensive rats. We were prompted to present our results here since pharmacological evaluation of our more extensive series emphasized different aspects of the activity profiles of these compounds and indicated poten-

tial therapeutic utility as neuroleptics or anti-Parkinson agents.

In general, the pharmacological outcome of replacing a piperidine by a piperazine ring in these 1,4-bis(indolylolethyl) compounds was to enhance central nervous system effects. Considerable control of the ratio of CNS and CVS activities was accomplished through variation of the number and positions of alkyl substituents in the indole and piperazine rings.

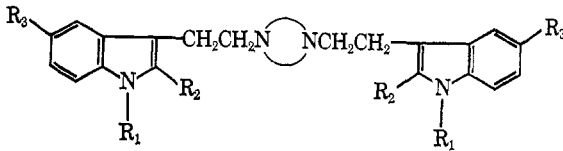



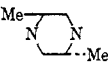
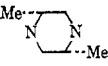


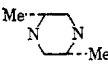
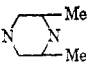
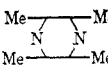
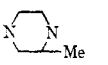
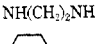


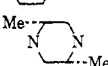
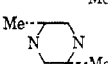


Chemistry. Two main synthetic approaches were adopted. Firstly, the convenient route to tryptamine derivatives established by Speeter and Anthony⁵ was employed, following the conditions used by Ames, *et al.*,⁶ for preparation of the indoleglyoxyloyl chlorides. These were then allowed to react with the appropriately substituted piperazines in 1,2-dimethoxyethane (DME) at room temperature to give the amides (Table I) in virtually quantitative yields; only bis products were produced even in the presence of excess piperazine. LiAlH₄ reduction of the amides was preferably carried out in DME to give the final products in high yield (Table II, method A). Alternatively, these final products could be obtained in one step by dialkylation of the piperazines with indol-3-ylethyl ha-

Table I. 1,4-Bis(indoleglyoxyloyl)piperazines

								
Compd	R ₁	R ₂	R ₃		Crystn solvent	% yield	Mp, °C	Formula ^e
1	H	H	H		DME ^a	97	>360	C ₂₄ H ₂₀ N ₄ O ₄ ^f
2	H	H	H		DMF ^b -H ₂ O	65	330 dec	C ₂₅ H ₂₂ N ₄ O ₄
3	H	H	H		DMF	63	361-362 dec	C ₂₆ H ₂₄ N ₄ O ₄ ^g
4	H	H	H		DMAC ^c -H ₂ O	52	337-339	C ₂₆ H ₂₄ N ₄ O ₄
5	H	H	H		DMF-H ₂ O	55	290-291	C ₂₈ H ₂₀ N ₄ O ₄ ·C ₃ H ₇ NO ^d
6	H	Me	H		DMF-H ₂ O	95	345-346 dec	C ₂₆ H ₂₄ N ₄ O ₄
7	H	Me	H		DMF-H ₂ O	44	342-343 dec	C ₂₈ H ₂₈ N ₄ O ₄
8	H	H	H		DMF-H ₂ O	18	342-343 dec	C ₂₀ H ₂₄ N ₄ O ₄
9	H	H	H		DMF-H ₂ O	55	322-324	C ₂₆ H ₂₈ N ₄ O ₄ ·0.5H ₂ O
10	H	H	H		DMF-H ₂ O	43	348-350 dec	C ₂₆ H ₂₂ N ₄ O ₄
11	H	H	H		DMF-H ₂ O	71	307-308 dec	C ₂₄ H ₂₂ N ₄ O ₄
12	H	H	Br		DMF-H ₂ O	70	>360	C ₂₄ H ₁₈ Br ₂ N ₄ O ₄
13	H	H	MeO		DMF-H ₂ O	46	365 dec	C ₂₆ H ₂₄ N ₄ O ₆ ·0.5H ₂ O

^a1,2-Dimethoxyethane. ^bN,N-Dimethylformamide. ^cN,N-Dimethylacetamide. ^dDMF solvate. ^eC, H, and N analyses were obtained on all compounds and were within ±0.4% of theory except where noted. ^fC: calcd, 67.28; found, 66.69. ^gC: calcd, 68.41; found, 68.92.

Table II. 1,4-Bis(indolyylethyl)piperazines

										
Compd	R ₁	R ₂	R ₃		Crystn solvent	% yield	Mp, °C	Formula ^a	Method	
14	H	H	H		EtOH-H ₂ O	72	195-197	C ₂₄ H ₂₈ N ₄	A, B	
15	H	H	H		C ₆ H ₆	66	107-108	C ₂₅ H ₃₀ N ₄	A	
16	H	H	H		DMAC	76	202-204	C ₂₆ H ₃₂ N ₄	A	
17	H	H	H		EtOH-H ₂ O	42	157-158	C ₂₆ H ₃₂ N ₄ ^b	A	
18	H	H	H		EtOAc	48	175-176	C ₂₈ H ₂₈ N ₄	A	
19	H	Me	H		DMF-H ₂ O	81	240-243	C ₂₆ H ₃₂ N ₄	A	
20	H	Me	H		DMF-H ₂ O	76	182-208	C ₂₆ H ₃₄ N ₄	A	
21	H	H	H		EtOH	97	174-176	C ₂₆ H ₃₂ N ₄	A	
22	H	H	H		EtOH	34	80-105	C ₂₈ H ₃₆ N ₄ ·C ₄ H ₄ O ₄ ·H ₂ O ^{c,d}	A	
23	H	H	H		EtOH-H ₂ O	36	100-107	C ₂₅ H ₃₀ N ₄	A	
24	H	H	H		EtOH	51	189-190	C ₂₄ H ₃₀ N ₄ ·2C ₄ H ₄ O ₄ ^e	A	
25	H	H	MeO		DMF-H ₂ O	23	210-211	C ₂₆ H ₃₂ N ₄ O ₂	A	
26	Me	H	H		EtOH	71	129-131	C ₂₆ H ₃₂ N ₄	C	
27	Me	H	H		n-Hexane	54	81-84	C ₂₈ H ₃₆ N ₄	C	
28	Me	Me	H		DMF-H ₂ O	85	176-178	C ₃₀ H ₄₀ N ₄	C	
29	Et	H	H		EtOH	97	125-127	C ₂₈ H ₃₆ N ₄	C	
30	C ₆ H ₅ CH ₂	H	H		EtOAc	68	158-161	C ₃₈ N ₄ O ₄	C	

^aC, H, and N analyses were obtained on all compounds and were within $\pm 0.4\%$ of theory except where noted. ^bC: calcd, 77.96; found, 77.47. ^cC: calcd, 68.30; found, 68.85. ^dFumarate. ^eMaleate.

lides in DMF at room temperature (method B).

Particular emphasis was placed on introducing an increasing number of alkyl substituents including stereoisomers where appropriate. Modifications to the piperazine ring included increasing the size (homopiperazine), introducing a fused phenyl ring (tetrahydroquinoxaline), and an open-chain variant (ethylenediamine). Substitution in the indole ring was achieved either by starting with the appropriately substituted monoindole intermediate or, in the case of N substituents, by alkylation of the corresponding N-unsubstituted bis compound (method C).

Biological Results. Renal hypertension was produced in female rats and their systolic blood pressure was recorded indirectly.⁷ Drugs were administered intraperitoneally to groups of four animals and pressures were recorded before and at 2 and 4 hr after dosing. Maximal effects usually occurred at 2 hr and are shown in Table III. The compounds were subjected to a battery of tests for evaluation of CNS properties,⁸ commencing with a pre-

liminary pharmacological assessment in which each compound was administered orally at four dose levels to groups of three mice. The animals were observed for at least 2 hr and Table III records the minimal doses causing decreased motor activity, ptosis, and hyperemia. Of particular interest among the more specific evaluation procedures were the results of tests for antimorphine⁹ and antitremorine¹⁰ activity which are also recorded in Table III. Compounds at four dose levels were administered orally to groups of six mice; the animals were then challenged with tremorine or morphine sulfate. Protection against tremors, salivation, lachrymation, and diarrhea in the former case, or the incidence of circling and "Straub-tail" in the latter, was determined by comparison with controls. For comparison the results obtained with chlorpromazine (a neuroleptic) and cogentin (an anti-Parkinson agent) in these tests are included in Table III. The parent unsubstituted compound 14 showed moderate antimorphine and antitremorine activity, as well as slight antihypertensive activity

Table III. Biological Activities^a

Compd	Antihypertensive		Prelim assessment ^{b,e}			Antimorphine ED ₅₀ ^b	Antitremorine/ ED ₅₀ ^b
	Dose ^b	Activity ^c	DMA ^d	Ptoxis	Hyperemia		
14	50	+	>400	>400	400	74	16
15	75	+++	12.7	40	400	200	>400
16	75	+	12.7	12.7	12.7	13	21
17	30	+++	4	4	12.7	17	21
18	60	±	>400	400	400	Syn ^g	Syn ^g
19	20	±	40	12.7	40	9.5	34
20	25	+	40	40	40	35	Syn ^g
21	60	+	12.7	0.4	12.7	2.6	31
22			127	40	127	120	118
23	60	±	12.7	1.27	12.7	4.5	15
24	40	++	>400	>400	>400	330	60
25			400	>400	>400	155	120
26	30	±	40	12.7	12.7	22	6.4
27	30	±	40	12.7	12.7	66	7
28			127	127	>400	320	240
29			40	40	400	350	47
30	75	±	127	>400	>400	>400	370
Chlorpromazine	5	++	12.7	4.0	>400	5.6	10.5
Cogentin			>400	>400	>400	20.5	1.39

^aSee test for experimental details. ^bDose expressed as mg/kg. ^cFalls in systolic pressure 2 hr after an intraperitoneal dose: >50 mm, +++; 50–30 mm, ++; 30–15 mm, +; <15 mm, ±. ^dDecreased motor activity. ^eMinimum effective oral dose. ^fED₅₀ for inhibition of tremors. ^gSynergistic.

(Table III) which increased to moderate activity when given orally at 100 mg/kg. Increasing the piperazine ring size enhanced the antihypertensive activity (15), as did introduction of *cis*-2,5-dimethyl substituents (17) or replacement of the piperazine ring by ethylenediamine (24). On the other hand, 2,6-dimethyl substitution in the piperazine ring (21) or 2-methyl substitution in the indole rings (19) caused marked antimorphine activity with only slight antihypertensive activity. Compounds showing marked antitremorine activity (26 and 27) both had methyl substituents on the indole nitrogens, and neither showed more than borderline antihypertensive activity.

Experimental Section

Melting points are uncorrected. Elemental analyses were within ±0.4% of the theoretical values except where noted in Tables I and II. Ir spectra supporting the structures were obtained for all compounds.

1,4-Bis(3-indoleglyoxyloyl)piperazine (1). Piperazine (2.6 g, 30 mmol) in dry 1,2-DME (100 ml) was stirred while 3-indoleglyoxyloyl chloride (4.3 g, 20 mmol) in 1,2-DME (25 ml) was added dropwise. The resulting precipitate was collected, suspended in H₂O, and stirred for 30 min, then collected again, washed with H₂O, and dried to give the product as a colorless solid (4.3 g).

Other 1,4-bis(3-indoleglyoxyloyl)piperazines in Table I were prepared in a similar manner, with recrystallization from DMF-H₂O when necessary.

1,4-Bis(indol-3-ylethyl)piperazine (14). Method A. Compound 1 (1.0 g, 2.25 mmol) was suspended in dry 1,2-DME (100 ml) and LiAlH₄ (1.0 g, 26 mmol) was added. The mixture was stirred under reflux for 24 hr. Excess LiAlH₄ was decomposed by dropwise addition of H₂O, the inorganic material was filtered off, and the filtrate was evaporated to give a colorless oil which crystallized on scratching. Recrystallization from EtOH-H₂O gave the product as colorless needles (0.6 g).

Other compounds in Table II prepared by method A were obtained in a similar manner.

Method B. A mixture of 3-(2-bromoethyl)indole (44.8 g, 0.2 mol), piperazine (8.6 g, 0.1 mol), and diisopropylamine (30.3 g, 0.3 mol) in DMF (200 ml) was stirred at room temperature for 18 hr. The precipitated diisopropylamine hydrobromide was filtered off and the filtrate was poured onto ice-water. A gum formed which solidified on scratching. The solid was collected, washed, dried, and recrystallized from EtOH-H₂O to give colorless needles of 1,4-bis(indol-3-ylethyl)piperazine (28.0 g).

1,4-Bis[2-(1-methyl-3-indolyl)ethyl]piperazine (26). Method C. Compound 14 (7.46 g, 20 mmol) was added to a stirred solution of sodium amide in liquid ammonia (500 ml). Methyl iodide (5.8 g, 41 mmol) in Et₂O (100 ml) was added dropwise to the stirred mixture; then the ammonia was allowed to evaporate overnight.

Et₂O (200 ml) was added to the residue, followed by H₂O (200 ml) added dropwise at first. The insoluble material (7.0 g) was collected, dried, and recrystallized from EtOH to give the product (5.7 g) as colorless needles. Compounds 27–30 were prepared in a similar manner.

Acknowledgment. The authors are indebted to Dr. M. I. Gluckman and Dr. T. Baum for permission to quote the biological results and to Dr. S. J. Childress for advice and encouragement.

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Chemical Conversion of the Psychotomimetic Amine 1-(2,5-Dimethoxy-4-methylphenyl)-2-aminopropane to 5-Hydroxy-2,6-dimethylindole

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Recent studies in a number of laboratories have described the unique pharmacologic properties of 2-(2,4,5-trihydroxyphenyl)ethylamine (1) commonly referred to as 6-hydroxydopamine.¹ When administered intravenously,