Notes

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

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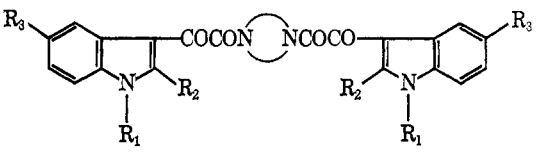
In a previous publication[1] we described a series of 1,4-bis(2-indol-3-ylethyl)piperidines possessing antihypertensive and central nervous system depressant activities. The pharmacological interest in that series prompted us to extend the work to include 1,4-bis(2-indol-3-ylethyl)piperazines and a considerable 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 metacorticoid 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 potential 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(indolylethyl) 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 Anthony[5] 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. $LiAlH_4$ 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-

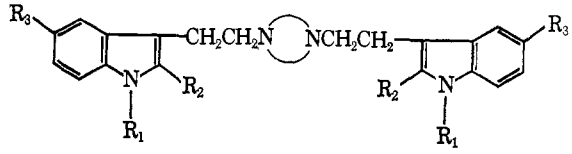
Table I. 1,4-Bis(indoleglyoxyloyl)piperazines



Compd	R_1	R_2	R_3	Crystn solvent	% yield	Mp, °C	Formula[e]
1	H	H	H	DME[a]	97	>360	$C_{24}H_{20}N_4O_4$[f]
2	H	H	H	DMF[b]–H_2O	65	330 dec	$C_{25}H_{22}N_4O_4$
3	H	H	H	DMF	63	361–362 dec	$C_{26}H_{24}N_4O_4$[g]
4	H	H	H	DMAC[c]–H_2O	52	337–339	$C_{26}H_{24}N_4O_4$
5	H	H	H	DMF–H_2O	55	290–291	$C_{28}H_{20}N_4O_4 \cdot C_3H_7NO$[d]
6	H	Me	H	DMF–H_2O	95	345–346 dec	$C_{26}H_{24}N_4O_4$
7	H	Me	H	DMF–H_2O	44	342–343 dec	$C_{28}H_{28}N_4O_4$
8	H	H	H	DMF–H_2O	18	342–343 dec	$C_{20}H_{24}N_4O_4$
9	H	H	H	DMF–H_2O	55	322–324	$C_{28}H_{28}N_4O_4 \cdot 0.5H_2O$
10	H	H	H	DMF–H_2O	43	348–350 dec	$C_{25}H_{22}N_4O_4$
11	H	H	H	DMF–H_2O	71	307–308 dec	$C_{24}H_{22}N_4O_4$
12	H	H	Br	DMF–H_2O	70	>360	$C_{24}H_{18}Br_2N_4O_4$
13	H	H	MeO	DMF–H_2O	46	365 dec	$C_{26}H_{24}N_4O_6 \cdot 0.5H_2O$

[a] 1,2-Dimethoxyethane. [b] *N*,*N*-Dimethylformamide. [c] *N*,*N*-Dimethylacetamide. [d] DMF solvate. [e] C, H, and N analyses were obtained on all compounds and were within ±0.4% of theory except where noted. [f] C: calcd, 67.28; found, 66.69. [g] C: calcd, 68.41; found, 68.92.

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



Compd	R_1	R_2	R_3	N N	Crystn solvent	% yield	Mp, °C	Formula[a]	Method
14	H	H	H		EtOH–H_2O	72	195–197	$C_{24}H_{28}N_4$	A, B
15	H	H	H		C_6H_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_2O	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_2O	81	240–243	$C_{26}H_{32}N_4$	A
20	H	Me	H		DMF–H_2O	76	182–208	$C_{28}H_{36}N_4$	A
21	H	H	H		EtOH	97	174–176	$C_{26}H_{32}N_4$	A
22	H	H	H		EtOH	34	80–105	$C_{28}H_{36}N_4 \cdot C_4H_4O_4 \cdot H_2O$[c,d]	A
23	H	H	H		EtOH–H_2O	36	100–107	$C_{25}H_{30}N_4$	A
24	H	H	H	$NH(CH_2)_2NH$	EtOH	51	189–190	$C_{24}H_{30}N_4 \cdot 2C_4H_4O_4$[e]	A
25	H	H	MeO		DMF–H_2O	23	210–211	$C_{26}H_{32}N_4O_2$	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_2O	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	$C_6H_5CH_2$	H	H		EtOAc	68	158–161	$C_{38}N_{40}N_4$	C

[a] C, H, and N analyses were obtained on all compounds and were within ±0.4% of theory except where noted. [b] C: calcd, 77.96; found, 77.47. [c] C: calcd, 68.30; found, 68.85. [d] Fumarate. [e] Maleate.

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 preliminary 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 antimorphine[9] and antitremorine[10] 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	Antitremorine[f]
	Dose[b]	Activity[c]	DMA[d]	Ptosis	Hyperemia	ED_{50}[b]	ED_{50}[b]
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

[a] See test for experimental details. [b] Dose expressed as mg/kg. [c] Falls in systolic pressure 2 hr after an intraperitoneal dose: >50 mm, +++; 50–30 mm, ++; 30–15 mm, +; <15 mm, ±. [d] Decreased motor activity. [e] Minimum effective oral dose. [f] ED_{50} for inhibition of tremors. [g] Synergistic.

(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 H_2O, and stirred for 30 min, then collected again, washed with H_2O, 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 recrystallisation from DMF–H_2O 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 $LiAlH_4$ (1.0 g, 26 mmol) was added. The mixture was stirred under reflux for 24 hr. Excess $LiAlH_4$ was decomposed by dropwise addition of H_2O, the inorganic material was filtered off, and the filtrate was evaporated to give a colorless oil which crystallized on scratching. Recrystallization from EtOH–H_2O 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–H_2O 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 Et_2O (100 ml) was added dropwise to the stirred mixture; then the ammonia was allowed to evaporate overnight. Et_2O (200 ml) was added to the residue, followed by H_2O (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.

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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,