Synthesis and Action on the Central Nervous System of Mescaline Analogues Containing Piperazine or Homopiperazine Rings

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Received December 29, 1981, from the **Medical Academy, Department of Drug Technology, Narutowicza 120a, 90145 Łódź, Poland,* the ‡*Department of Chemistry, Northwestern University, Evanston, IL 60201,* and the §*Medical Academy, Department of Pharmacodynamics, Narutowicza 120a, 90145 Łódź, Poland.* Accepted for publication March 29, 1982.

Abstract □ Structural juxtaposition of the 3,4,5-trimethoxyphenyl group in the same molecule with a piperazine or homopiperazine ring has been realized in a series of mescaline analogues (I–IV) as part of an investigation into the pharmacological properties of the seven-membered perhydro-1,4-diazepines (homopiperazines). The analogous six-membered piperazines were synthesized and tested as reference substances to determine whether the seven-membered ring conveyed special properties. A variety of pharmacological tests of action on the CNS showed that replacement of the amino group in mescaline by the heterocycles significantly alters the biological activity. In particular, both the piperazine and the homopiperazine derivatives displayed sedative activity to about the same extent.

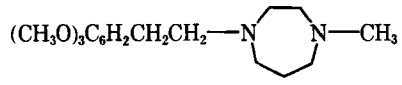
Keyphrases □ Mescaline analogues—synthesis and action on the CNS, containing piperazine or homopiperazine rings □ CNS agents—synthesis and action of mescaline analogues containing piperazine or homopiperazine rings □ Piperazine rings—mescaline analogues, synthesis and action on the CNS □ Homopiperazine rings—mescaline analogues, synthesis and action on the CNS

The 3,4,5-trimethoxyphenyl moiety attached to an amino nitrogen through a two- or three-carbon bridge is well known as a pharmacophoric group in drugs that possess sedative, hypotensive, antiarrhythmic, and vasodilating properties (1). Furthermore, there are numerous commercial drugs containing the piperazine ring, and a few with the perhydro-1,4-diazepine (homopiperazine) ring. At least two drugs contain both the homopiperazine ring and the trimethoxyphenyl group: 1-methyl-4-(3,4,5-trimethoxybenzoyloxy)methylhomopiperazine, an antihypertensive agent, and 1,4-bis[3-(3,4,5-trimethoxybenzoyloxy)propyl]homopiperazine (dilazep), a coronary vasodilator.

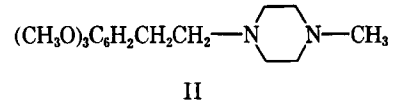
Mescaline, 2-(3,4,5-trimethoxyphenyl)ethylamine [3,4,5-$(CH_3O)_3C_6H_2CH_2CH_2NH_2$], a simple trimethoxyphenyl derivative, has been known as an hallucinogen and an agent on the CNS. The present study explored the biological effects on the CNS of a molecule that closely juxtaposes the trimethoxyphenyl group with the homopiperazine ring. This arrangement was obtained by replacing the amino group in mescaline with the homopiperazine ring. The piperazine analogue also was examined for comparison. These lines of inquiry were suggested by earlier investigations on the conformational (2, 3) and pharmacological (4) properties of homopiperazines.

DISCUSSION

The synthetic objective was attachment of the heterocycles, piperazine or homopiperazine, through a bismethylene fragment to the trimethoxyphenyl group. One approach attached the heterocycle to the bismethylene carbon through one nitrogen, and the second nitrogen carried a methyl group (compounds I and II, respectively). In another approach, both nitrogens of the heterocycles were supplied with the trimethoxyphenyl substrate (compounds III and IV, respectively). The synthesis of these four molecules began with 3,4,5-trimethoxyphenylacetic acid [3,4,5-$(CH_3O)_3C_6H_2CH_2CO_2H$].



I



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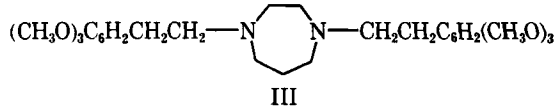
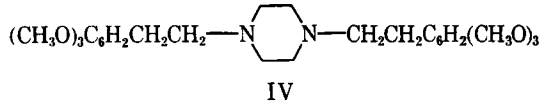


III



IV

Reduction of the corresponding methyl ester and treatment with thionyl chloride produced the chloride, 3,4,5-$(CH_3O)_3C_6H_2CH_2CH_2Cl$, which was allowed to react with the cyclic amines to give the four desired compounds, 1-methyl-4-[2-(3,4,5-trimethoxyphenyl)ethyl]perhydro-1,4-diazepine (I); 1-methyl-4-[2-(3,4,5-trimethoxyphenyl)ethyl]piperazine (II); 1,4-bis[2-(3,4,5-trimethoxyphenyl)ethyl]perhydro-1,4-diazepine (III); and 1,4-bis[2-(3,4,5-trimethoxyphenyl)ethyl]piperazine (IV). Alternatively, the ester, 3,4,5-$(CH_3O)_3C_6H_2CH_2CO_2CH_3$, was converted through the acid chloride to the amide containing the heterocycle, and the amide was reduced to the desired product. The structures of all products were confirmed by spectral and elemental analysis.

The four compounds were used in nine separate tests of pharmacological activity. In several tests, the dose level as a ratio of the LD_{50} was varied. No differences were found between the control group, which received doses of 0.9% NaCl, and the groups that received doses of compounds I–IV, for the following properties: body temperature, behavioral despair, central action of 3-(3,4-dihydroxyphenyl)-L-alanine (levodopa), apomorphine-induced stereotypy, or convulsant action of pentylenetetrazol. None of the compounds eliminated the aggressiveness of isolated mice. Quantitative data for apomorphine behavior are given in Table I. Other negative results are omitted. Thus, these compounds do not exhibit activity typical of tranquilizers.

Positive, dose-related results for three other tests are listed in Table I. All four tested compounds prolonged sleeping time and inhibited locomotor activity in mice. Reduction in amphetamine-induced locomotor stimulation was observed in mice for all four compounds, but the results are significant at the 95% level only for I and II, which contain a single

0022-3549/83/0300-0304$01.00/0

Table I—Pharmacological Results on Heterocyclic Analogues of Mescaline

Compound	LD_{50}, mg/kg ip	Dose, Ratio of LD_{50}	Spontaneous Locomotor Activity, Count/30 min (n = 10)	Amphetamine Hyperactivity, Counts/30 min (n = 10)	Hexobarbital Sleeping Time, min (n = 10)	Apomorphine Behavior Mean Scores (n = 6)	
						Excitation	Stereotyped Behavior
0.9% NaCl[a]			185 ± 20.1[b]	418 ± 55	18.1 ± 1.4	4.0 ± 0.85	7.6 ± 1.3
I	685 ± 170[b]	0.1	120 ± 13.3[c]	236 ± 40[c]	33.7 ± 2.2[e]	4.0 ± 0.75	7.5 ± 1.8
		0.05	175 ± 19.7	421 ± 52	23.0 ± 2.5		
II	660 ± 172	0.1	115 ± 19.0[c]	251 ± 38[c]	41.4 ± 4.0[e]	4.2 ± 0.92	6.8 ± 2.4
		0.05	181 ± 23.2	385 ± 48	28.6 ± 3.0[d]		
		0.025			17.2 ± 1.6		
III	330 ± 87	0.1	112 ± 17.0[c]	310 ± 54	38.4 ± 2.1[e]	4.3 ± 0.72	7.7 ± 2.1
		0.05	195 ± 22.3	405 ± 48	28.4 ± 3.2[d]		
		0.025			21.7 ± 2.3		
IV	305 ± 65	0.1	115 ± 20.0[c]	286 ± 40	36.5 ± 1.6[e]	4.4 ± 0.81	7.4 ± 2.2
		0.05	184 ± 22.4	398 ± 47	26.8 ± 2.9[d]		
		0.025			19.0 ± 2.0		

[a] Control group. [b] Standard error of the mean. [c] A significant difference from the control at the 95% confidence level. [d] A significant difference from the control group at the 99% confidence level. [e] A significant difference from the control at the 99.9% confidence level.

trimethoxyphenyl residue. Thus, the results of these tests indicate that I–IV exhibit sedative activity.

The presence of the piperazine or homopiperazine ring in place of the simple amino group in mescaline significantly alters the effect of the compound on the CNS. Within this group of compounds, there was little difference in sedative activity between the six- and seven-membered rings. Previously tested (5) homopiperazine-containing compounds, which were esters or amides of *p*-chlorobenzoic acids, did not exhibit a depressive effect on the CNS. Consequently, the sedative activity of I–IV is caused at least in part by the presence of the 3,4,5-trimethoxyphenylethyl moiety. Since neither mescaline nor *N,N*-dimethylmescaline (6) exhibits this behavior, it was concluded that the sedative activity requires both the trimethoxyphenyl group and the cyclic, tertiary amine.

EXPERIMENTAL

Chemistry—Melting points (uncorrected) were determined in open glass capillaries[1]. IR spectra were obtained on a scanning spectrophotometer[2], either as a neat thin film or as potassium bromide disks. NMR spectra were recorded[3] with respect to tetramethylsilane. Mass spectra[4] were obtained by direct injection. Microanalysis[5] for carbon, hydrogen, and nitrogen were within 0.4% of calculated values. Piperazine, 1-methylpiperazine, homopiperazine, and 3,4,5-trimethoxyphenylacetic acid were commercially available[6]. 1-Methylhomopiperazine was prepared according to the literature (7).

2-(3,4,5-Trimethoxyphenyl)ethanol—Trimethoxyphenylacetic acid[6] was converted to its ester, which was reduced according to a previous method (8), with a change in the ratio of lithium aluminum hydride to 1.5 moles/mole of the methyl-3,4,5-trimethoxyphenylacetate: 76% yield, bp 160–164°/0.8 mm Hg.

Anal.—Calc. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.02; H, 7.55.

1-Chloro-2-(3,4,5-trimethoxyphenyl)ethane — 1-Chloro-2-(3,4,5-trimethoxyphenyl)ethane was prepared by treatment of the alcohol with thionyl chloride in pyridine (8): 74% yield, bp 158–160°/0.8 mm Hg.

Anal.—Calc. for $C_{11}H_{15}ClO_3$: C, 57.27; H, 6.55. Found: C, 57.01; H, 6.48.

3,4,5-Trimethoxyphenylacetyl Chloride — 3,4,5-Trimethoxyphenylacetic acid[6] (17.8 g, 0.15 mole) was added to a benzene solution (100 ml) of thionyl chloride (22.6 g, 0.1 mole). The reaction mixture was heated to reflux until evolution of sulfur dioxide ceased. Benzene and excess thionyl chloride were removed by rotary evaporation, and the residue was distilled to give 16.2 g (72.3%) of the product: bp 154–156°/1 mm Hg, mp 96–98° (from petroleum ether).

Anal.—Calc. for $C_{11}H_{13}ClO_4$: C, 53.99; H, 5.35. Found: C, 53.55; H, 5.25.

1-Methyl-4-(3,4,5-trimethoxyphenylacetyl)perhydro-1,4-diazepine—The acid chloride (4 g, 0.016 mole) was added dropwise with boiling to a benzene solution (50 ml) of 1-methylhomopiperazine (1.82 g, 0.016 mole) and sodium carbonate (2.1 g, 0.02 mole). Stirring and heating were continued for 3 hr, and the hot reaction mixture was filtered from the inorganic salts. The solvent was removed by rotary evaporation, and the residue was recrystallized from diethyl ether–benzene: 2.6 g, 50% yield, mp 111–114°; NMR (chloroform-*d*) δ 1.85 (m, 2H, CCH_2C), 2.29 (s, 3H, NCH_3), 2.50 (m, 4H, $RNCH_2$), 3.58 (m, 6H, $CONCH_2$), 3.82 (s, 9H, OCH_3), and 6.5 (s, 2H, aromatic); IR (KBr) 3050, 1670, and 1620 cm^{-1}.

Anal.—Calc. for $C_{17}H_{26}N_2O_4$: C, 63.33; H, 8.13; N, 8.69. Found: C, 63.20; H, 8.21; N, 8.90.

1-Methyl-4-[2-(3,4,5-trimethoxyphenyl)ethyl]perhydro-1,4-diazepine (I)—In a dropwise fashion, 1-chloro-2-(3,4,5-trimethoxyphenyl)ethane (10 g, 0.04 mole) in 75 ml of a 1:1 solution of toluene–dimethylformamide was added to a refluxing solution of toluene (75 ml) and dimethylformamide (75 ml) containing 1-methylhomopiperazine (4.5 g, 0.04 mole) and anhydrous potassium carbonate (11.04 g, 0.08 mole). Stirring and heating were continued for 14 hr. The inorganic salts were filtered, and the solvents were removed by rotary evaporation. The residue was distilled to give 6.5 g (52.7%) of the product: bp 175–190°/0.2 mm Hg, n_D^{20} 1.5365; NMR (chloroform-*d*): δ 1.85 (m, 2H, CCH_2C), 2.42 (s, 3H, NCH_3), 2.77 (m, 12H, CH_2), 3.88 (s, 9H, OCH_3), 6.47 (s, 2H, aromatic); IR (film) 3050, 1620, and 1520 cm^{-1}.

The dihydrochloride was prepared by acidification of I in absolute diethyl ether with an ether solution of anhydrous hydrogen chloride: mp 240–241°.

Anal.—Calc. for $C_{17}H_{30}Cl_2N_2O_3$: C, 53.54; H, 7.93; N, 7.35. Found: C, 53.23; H, 7.67; N, 7.20.

Reduction of 1-methyl-4-(3,4,5-trimethoxyphenylacetyl)perhydro-1,4-diazepine with lithium aluminum hydride in tetrahydrofuran afforded I (45%) that was identical chemically and spectroscopically to the material obtained above.

1-Methyl-4-[2-(3,4,5-trimethoxyphenyl)ethyl]piperazine (II)—Treatment of 1-chloro-2-(3,4,5-trimethoxyphenyl)ethane with piperazine[6] in a manner analogous to the preparation of I produced II: 6.3 g, 53.5% yield, bp 174–184°/0.2 mm Hg, n_D^{20} 1.5335; NMR (chloroform-*d*): δ 2.38 (m, 15H, CH_3/CH_2), 3.79 (s, 9H, OCH_3), and 6.38 (s, 2H, aromatic); IR (film) 3050, 1620, 1510, and 1150 cm^{-1}. The dihydrochloride was prepared as described for I, mp 257–258° dec.

Anal.—Calc. for $C_{16}H_{28}Cl_2N_2O_3$: C, 52.32; H, 7.68; N, 7.63. Found: C, 52.01; H, 7.61; N, 7.45.

1,4-Bis[2-(3,4,5-trimethoxyphenyl)ethyl]perhydro-1,4-diazepine (III)—To a refluxing solution of toluene (75 ml) and dimethylformamide (75 ml) containing homopiperazine[6] (1.5 g, 0.015 mole) and anhydrous potassium carbonate (8.26 g, 0.06 mole) was added 1-chloro-2-(3,4,5-trimethoxyphenyl)ethane (7.0 g, 0.03 mole) in 50 ml of 1:1 toluene–dimethylformamide, in a dropwise fashion. Stirring and heating were continued for 14 hr. The inorganic salts were filtered, and the solvents were removed by rotary evaporation. The thick, oily residue (7 g, 95% yield) appeared by spectroscopy to be pure but failed to crystallize. It was purified as the hydrochloride, which was prepared as described for I: 6 g, 75% yield, mp 198–200° (absolute methanol–diethyl ether); NMR (chloroform-*d*): δ 1.80 (m, 2H, CCH_2C), 2.68 (m, 16H, CH_2), 3.71 (s, 18H, OCH_3), and 6.32 (s, 4H, aromatic); IR (film of crude product) 3050, 1600, 1510, and 1130 cm^{-1}.

Anal.—Calc. for $C_{27}H_{42}Cl_2O_6N_2$: C, 57.75; H, 7.54; N, 4.99. Found: C, 57.55; H, 7.34; N, 4.57.

[1] Electrothermal Ltd., Deer Park, N.Y.
[2] Unicam SP 200G, England.
[3] Varian EM-360 Spectrometer, Varian Associates, Palo Alto, Calif.
[4] LKB 2091, LKB Instruments, Rockville, Md.
[5] Medical Academy, Łódź, Poland.
[6] Aldrich Chemical Co., Milwaukee, Wis.

1,4-Bis[2-(3,4,5-trimethoxyphenyl)ethyl]piperazine (IV)—Compound IV was prepared in the same manner as described for III, but with piperazine[6]. After evaporation of the solvents, the residue crystallized from 1:1 diethyl ether–petroleum ether: 2.3 g, 32% yield, mp 120–122°; NMR (chloroform-*d*): δ 2.65 (s, 16H, CH_2), 3.87 (s, 18H, OCH_3), and 6.41 (s, 4H, aromatic). IR (KBr) 3040, 1620, 1500, and 1160 cm^{-1}. The dihydrochloride was prepared as described for I: mp 259–260° dec.

Anal.—Calc. for $C_{26}H_{40}O_6N_2Cl_2$: C, 57.03; H, 7.36; N, 5.12. Found: C, 56.85; H, 7.23; N, 5.01.

Pharmacology—The experiments were performed on male Swiss white mice (18–26 g) and male Wistar rats (150–180 g). The investigated compounds were administered intraperitoneially in aqueous solutions.

The LD_{50} values were determined by a previous method (9).

The effect of I–IV on locomotor activity in normal and amphetamine-treated mice was recorded throughout 30-min sessions in photoresistant cages. The investigated compounds (administered intraperitoneally) and amphetamine (5 mg/kg sec) were administered 60 and 30 min, respectively, before testing.

The effect on the apomorphine-induced stereotypy was investigated in rats. Apomorphine (1.25 mg/kg sec) was injected 60 min after the tested compounds.

For the effect on sleeping time in mice, hexobarbital (70 mg/kg ip) was injected 60 min after the test compounds.

Anticonvulsant activity was investigated by the minimal and maximal pentylenetetrazol shock (pentylenetetrazol, 80 and 50 mg/kg sc, respectively). The number of animals protected against clonic convulsions in minimal shock or tonic extensions of limbs in maximal shock was registered.

The effect on behavioral despair in mice was examined by a previous method (10). The compounds were injected 60 min before examination.

The effect on the central action of 3-(3,4-dihydroxyphenyl)-L-alanine (levodopa) was tested on mice by modifications of a previous method (11). The alanine (100 mg/kg) was injected 4 hr after pargyline (40 mg/kg po) and 1 hr after the investigated compounds.

The effect on the aggressiveness of isolated (3 weeks) mice was examined by a previous method (12). Behavior was tested at 1-hr intervals for 4 hr.

Rectal body temperature in mice was measured with a thermometer for 3 hr after administration of the test compounds.

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ACKNOWLEDGMENTS

This work was supported by the National Institutes of Health (Grant R01 GM26124) and by the Polish Academy of Sciences (Problem I.12).

Phenytoin I: *In Vitro–In Vivo* Correlation for 100-mg Phenytoin Sodium Capsules

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Abstract □ *Dissolution profiles for 11 brands of phenytoin sodium capsules were carried out by the basket and paddle methods (USP) and the spin-filter method. The results from the dissolution studies have been correlated with observed differences in in vivo parameters (C_{max} and t_{max}). The dissolution by the basket method at 50 rpm in water gave a correlation >0.9. The results suggest the existence of two types of phenytoin sodium products on the market.*

Keyphrases □ Phenytoin—*in vitro–in vivo* correlation for sodium phenytoin capsules, dissolution □ Dissolution—*in vitro–in vivo* correlation for sodium phenytoin capsules □ *In vitro–in vivo* correlation—sodium phenytoin capsules, dissolution

Increasing evidence has been presented in the scientific literature which show correlations between the *in vivo* performance of formulations and their *in vitro* dissolution behavior (1–3). To obtain an *in vitro–in vivo* correlation for any product, two criteria are essential: (*a*) the differences in *in vivo* parameters such as *AUC*, t_{max}, C_{max}, or C_p at a time among different lots tested and (*b*) differences in the *in vitro* dissolution rates of the same products. In cases where differences are observed in *in vivo* behavior, the *in vitro* parameter can be altered to optimize the correlation with *in vivo* data. This is achieved by varying such parameters as dissolution methodology, dissolution medium, rate of agitation, *etc.* In many instances, it has been possible to obtain correlations with *in vivo* data where a discriminating and reproducible *in vitro* test is employed (1–3). *In vitro–in vivo* correlations can generally be achieved with any reproducible method provided the proper selection of medium and the degree of agitation are made so as to permit discrimination among drug products. The key elements are reproducibility of the method, proper choice of medium, and degree of agitation.

Phenytoin is a commonly used anticonvulsant drug and has been classified as a drug with high risk potential with

0022-3549/83/0300-0306$01.00/0