Troponoids. 6.[1] Troponylpiperazines: A New Class of Dopamine Agonists

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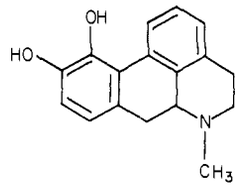
Received April 4, 1983

A series of alkyltroponylpiperazine derivatives was synthesized and evaluated for dopaminergic activity in rats rendered hypokinetic by the bilateral injection of 6-hydroxydopamine (6-OHDA) into the anterolateral hypothalamus. Several members of the series were active, and a structure–activity relationship is presented. A few selected compounds were also evaluated with regard to their ability to induce contralateral rotational behavior in rats with a unilateral 6-OHDA-induced lesion of the nigrostriatal dopamine pathway. The compounds were compared to bromocriptine. The results indicate that dopaminergic activity is very sensitive to small changes in the troponylpiperazine moiety.

During the past decade a new class of pharmacological agents have emerged, the so-called dopaminergic agonists, which, as their name implies, stimulate central and peripheral dopamine (DA) receptors, causing widespread motor, behavioral, endocrine, and blood pressure lowering effects. One area in which these drugs are therapeutically effective is Parkinson's disease, which is characterized by a decrease in dopaminergic activity in the nigro-striatal–pallidal complex.[2]

Apomorphine (1), the classical DA agonist, was demonstrated to exert anti-Parkinson activity as early as 1951.[3] However, its short duration of action and its side effects, especially nausea and hypotension, seriously limited its use as a practical form of therapy.



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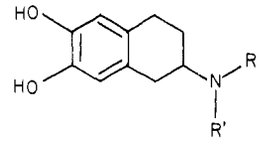

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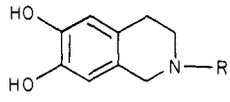

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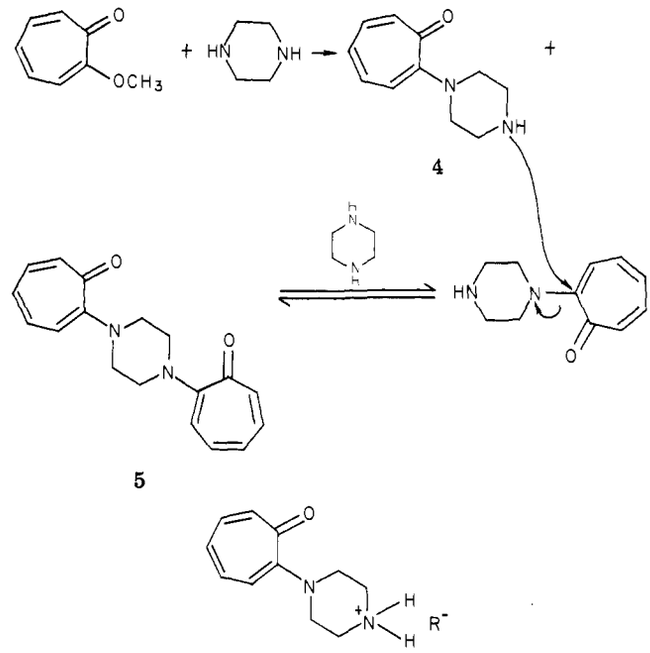
Compounds that were experimentally and/or clinically evaluated in the past as potential DA agonists were (a) derivatives of apomorphine,[4,5] (b) semirigid compounds where the DA moiety was incorporated into the molecule with trans (2) or cis (3) configurations of the side chain,[6] and (c) established[7] or newer[8] ergot derivatives.

The present study describes the synthesis and pharmacological evaluation of chemically novel troponylpiperazine derivatives as potential DA agonists.

Chemistry. In general, the troponylpiperazines can be readily obtained by the reaction of mono-N-substituted piperazines with 2-methoxytropone. When suitably substituted piperazines were not accessible, it was deemed convenient to prepare troponylpiperazine 4 and then alkylate the secondary nitrogen in a conventional manner (Scheme I).

Condensation of 2-methoxytropone with piperazine proceeded smoothly to yield 4 as a major product with a small amount of ditroponyl derivative 5. The attempts to obtain 4 completely free of 5 failed. It was observed that when an eluate (from chromatography) containing 4 completely free of 5 was evaporated under vacuum, 5 appeared in the residue. Furthermore, when a solution of pure ditroponyl derivative 5 was heated in piperazine to 110 °C, it was essentially completely transformed to compound 4. These transformations may be explained as shown in Scheme I.

Scheme I



6, R = CH_3COO
7, R = CH_2SO_2

When the crude reaction mixture was acidified with acetic acid, the acetate salt 6 was satisfactorily isolated by chromatography as a brown oil. On the other hand, when the filtrate of the reaction mixture, after the removal of

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(1) For Part 5, see: Ahmed, F. R.; Bagli, J. *Can. J. Chem.* **1982**, *60*, 2687.
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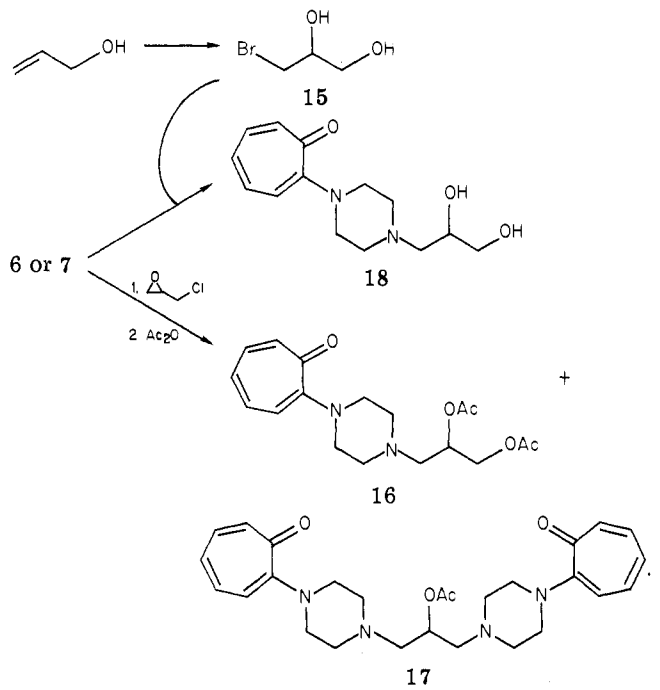
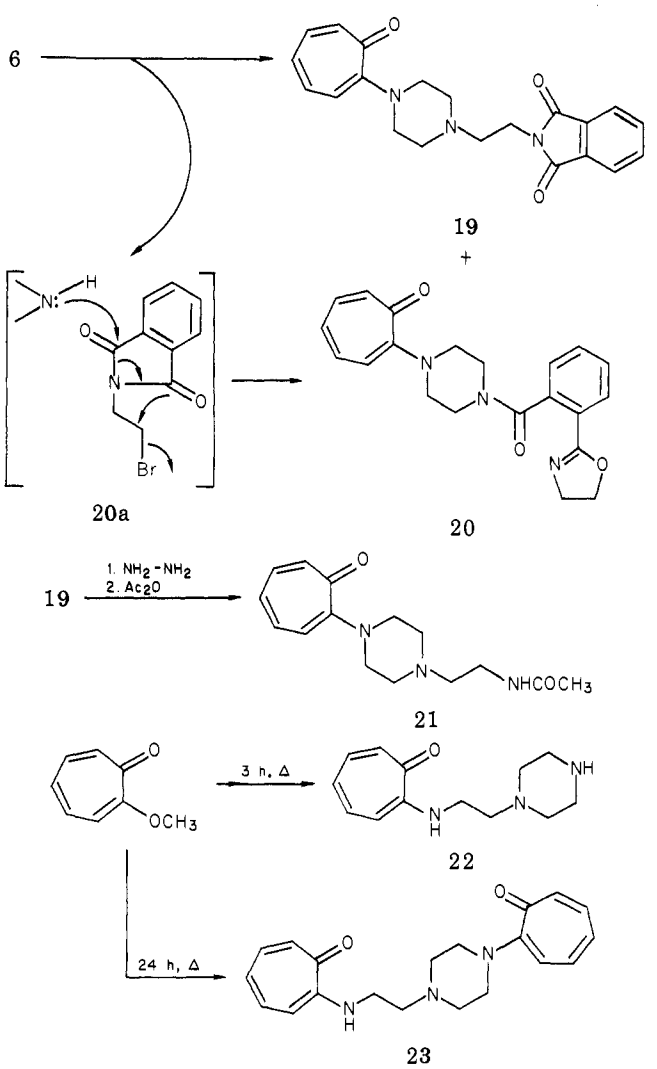
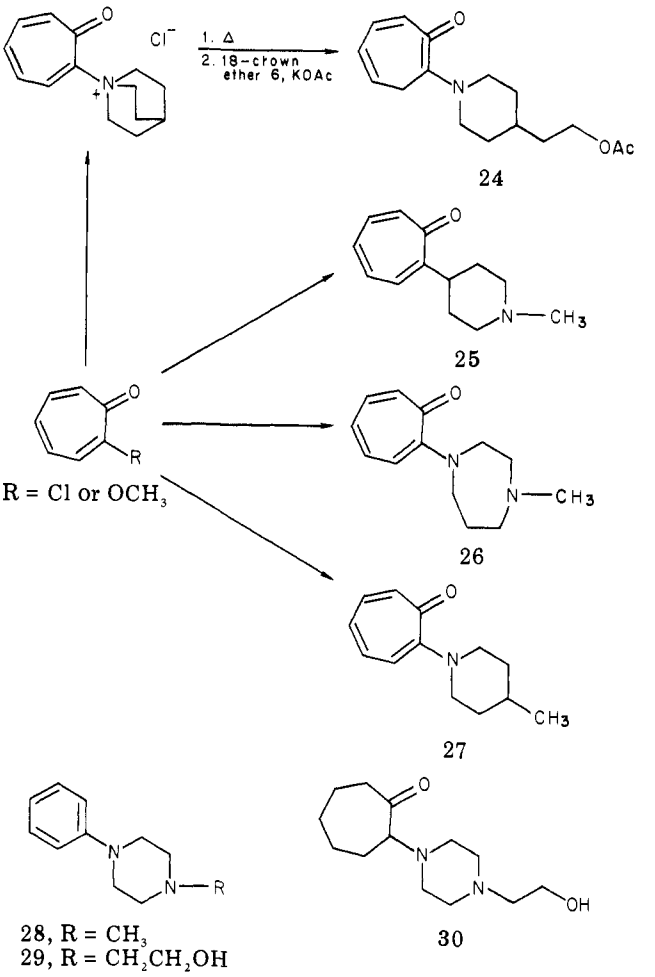
Scheme II



Scheme III



Scheme IV



a major portion of **5**, was acidified with methanesulfonic acid, the corresponding mesylate was obtained as a yellow crystalline solid. These salts were used in the subsequent alkylation reaction to generate compounds **9–12** and **14** (Table I). Compound **13** was prepared by condensation of *tert*-butylpiperazine[9] with 2-methoxytropone. Compounds **37**, **41–44**, and **46** were synthesized by reacting appropriately halogenated substrates with either acetate **6** or mesylate **7**. Esterification of **35** with the appropriate acyl halide yielded compounds **39** and **40**. Condensation of acetate **6** with chloroacetone and 2-bromobutan-3-one, followed by sodium borohydride reduction, yielded compounds **36** and **38**, respectively. Hydration of nitrile **46** with concentrated sulfuric acid gave the amide **45**.

The reaction of epichlorohydrin with acetate salt **6** led to a mixture of products (Scheme II), which upon acetylation gave in low yield compounds **16** and **17**. The dihydroxy derivative **18** was prepared by condensation of salt **7** with 1-bromopropane-2,3-diol (**15**).

Condensation of acetate salt **6** with *N*-(2-bromoethyl)-phthalimide led to the isolation of two products, the structures of which were assigned as **19** and **20** based on spectroscopic analysis (Scheme III). Formation of compound **20** can be rationalized by considering a nucleophillic attack by piperazine as shown in **20a**. Hydrazinolysis of **19** led to the desired primary amine. This compound slowly decomposed at room temperature. Acetylation yielded stable crystalline acetamide **21**.

The reaction of *N*-(ethylamino)piperazine with 2-methoxytropone yielded, after refluxing for 3 h in methanol, compound **22**, but when heating was continued for

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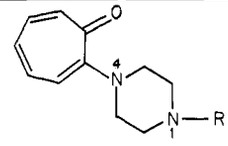
Table I. Effect of *N*-Alkyltroponylpiperazines on 6-OHDA-Induced Hypokinesia in Rats



compd	R	mp, °C	crystn solv[d]	formula	anal.	dose, mg/kg sc	cumulative ambulation score, means ± SEM
4[a]	H	174–176	A	$C_{11}H_{14}N_2O\cdot CH_3SO_3H$	C, H, N	50	55 ± 5.8 (5)[f]
8[b]	CH_3	118–120	A/E	$C_{12}H_{16}N_2O\cdot C_4H_4O_4$	C, H, N	50	278 ± 57 (6)
9	CH_2CH_3	oil		$C_{13}H_{18}N_2O$	C, H, N	50	70 ± 15 (5)
10	$(CH_2)_2CH_3$	oil		$C_{14}H_{20}N_2O$[e]		50	159 ± 33 (6)
11[c]	$(CH_2)_3CH_3$	192–194	Ea/E	$C_{15}H_{22}N_2O\cdot HCl\cdot H_2O$	C, H, N	50	inactive
12	$CH(CH_3)_2$	51.5–52.5	H	$C_{14}H_{20}N_2O$	C, H, N	50	431 ± 113 (6)
13[b]	$C(CH_3)_3$	160–162	E/M	$C_{15}H_{22}N_2O\cdot C_4H_4O_4$	C, H, N	50	inactive
14[b]	$CH_2CH(CH_3)_2$	120–121	M/E	$C_{15}H_{22}N_2O\cdot C_4H_4O_4$	C, H, N	25	372 ± 60 (4)
bromocriptine						10	112 ± 23 (12)

[a] Characterized and tested as the methanesulfonate salt. [b] Characterized and tested as the maleate salt. [c] Characterized and tested as the hydrochloride salt. [d] A = acetone; H = hexane; E = ether; M = methanol; Ea = ethyl acetate. [e] This compound was characterized by IR, UV, NMR, and MS. [f] Numbers in parentheses refer to number of rats in each group.

24 h, product **23** was isolated.

In an effort to establish the structural requirement for dopaminergic activity of the troponylpiperazines, modifications were incorporated at certain positions (Scheme IV). The reaction of quinuclidine with 2-substituted tropone is reported.[10] The compound obtained from the reaction of 2-chlorotropone and quinuclidine was pyrolytically opened, and the chlorine was replaced by acetate with potassium acetate–18-crown ether-6,[11] to generate **24**. Compound **25** was obtained in low yield by condensation of (*N*-methylpiperidin-4-yl)magnesium chloride[12] with 2-methoxytropone. The products **26–29** were obtained in the conventional manner with appropriate monosubstituted heterocyclic bases. Catalytic hydrogenation of **35** gave the alcohol **30**.

Results and Discussion

Dopamine receptor agonists exert a variety of pharmacological effects,[13] the most characteristic being the ones that occur in animal models that mimic the Parkinsonian syndrome.

The hypokinetic rat model, which has been used in the present study, fulfills this criterion. The abnormal behavior,[14] the denervation of catecholaminergic pathways,[15] the loss of neurotransmitter from nerve terminals,[15] and the development of postsynaptic DA receptor supersensitivity,[16] which are all brought about by the bilaterial injection of 6-OHDA, resemble the clinical, pathological, and biochemical manifestations as well as the compensatory mechanisms[17] of Parkinson's disease. The experimentally induced hypokinesia is reversed by several direct-acting DA agonists,[15,16,18] while amphetamine, which acts by releasing endogenous catecholamines, is inactive.[15]

We have evaluated 38 troponylpiperazine derivatives in hypokinetic rats; the results are shown in Tables I–III and discussed in detail in the structure–activity section. While several of the compounds showed activity, none of them were as active as bromocriptine on a milligram per kilogram basis.

Three of the active compounds were also evaluated in rats with a unilaterally degenerated nigro-striatal pathway. In such rats, DA agonists induce contralateral rotational behavior, which is brought about by the development of postsynaptic DA receptor supersensitivity in the denervated striatum.[19] Table IV illustrates that compounds **8**, **35**, and **39** induced contralateral rotational behavior, both the intensity and duration of which were dose-dependent. However, the potency of bromocriptine was greater and its duration of action longer than that of the troponylpiperazines.

Haloperidol antagonized the turning behavior induced by compound **35** in a dose-dependent manner (Table V). This finding supports the claim that the novel troponylpiperazines act through dopaminergic mechanisms.

Structure–Activity Relationships. Most of the potential dopaminergic agonists reported to date have a 3,4-dihydroxyphenethylamine moiety incorporated in their molecules. This is true for the semirigid derivatives of types **2** and **3**, as well as for the more recently reported tricyclic analogues[20] of **31**, and the vascular dopamine agonist[21] SKF38393 (**32**). In contrast, bromocriptine[22] (**33**), RO-8-4650[23] (**34**), and monosubstituted 2-aminotetralin derivatives,[6b] such as **34a**, represent examples where the

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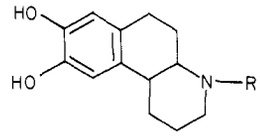

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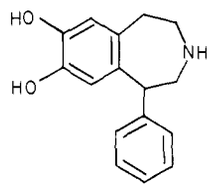

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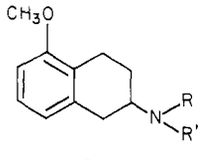
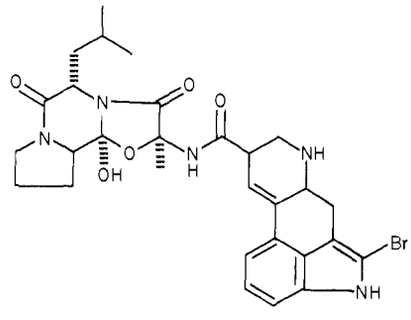


34a



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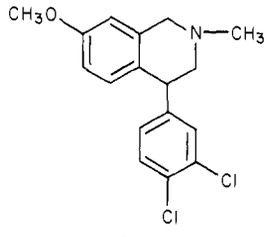

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nonsubstituted or monosubstituted phenethylamine moiety constitutes part of the molecule. The troponylpiperazines, described in the present paper, represent a series of compounds that do show dopamine agonist activity in the absence of a phenethylamine moiety in the molecule.

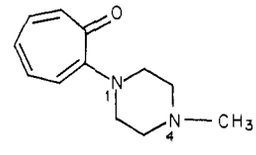
The effect of N-alkylation on dopamine agonist activity in the dopamine,[24] apomorphine,[25] and 2-amino-6,7-dihydroxytetrahydronaphthalene[6b] (ADTN, **2**) molecules is well documented and suggests that agonistic activity reaches a maximum with an *n*-propyl substituent and drops sharply upon further homologation. In the case of the troponylpiperazines, dopaminergic activity in general was greater in the lower *N*-alkyl-substituted derivatives than in the NH derivative (**4**) (Table I). While the N-C_2H_5 (**9**) derivative was only slightly more active than NH (**4**), both the N-CH_3 (**8**) and the *N*-*n*-propyl (**10**) derivatives showed considerably enhanced activity. In contrast, the *N*-*n*-butyl compound (**11**) was completely inactive at the maximum dose (50 mg/kg sc) used to evaluate other derivatives of this series. Whereas branched-chain alkyl derivatives have been reported to be devoid of dopaminergic activity in the ADTN series,[6b,20] in the troponylpiperazine series the ambulation scores increased several fold going from N-C_2H_5 (**9**) to *N*-isopropyl (**12**). Similarly, a significant increase in activity was noted when the *n*-propyl (**10**) substituent was changed to a *sec*-butyl (**14**) substituent. A carbon atom α to the nitrogen is often vulnerable to oxidative metabolic changes. Substitution of the proton of the methylene α to the nitrogen atom (see **12**) by a methyl group is known to render the molecule resistant to this metabolic change.[26] This may explain the enhanced activity of **12** and **14**. In a recent report,[27] α-methyldopamine derivatives were shown to be more active than their desmethyl counterparts in inducing locomotor activity. The response was seen only after intra-accumbens but not upon peripheral administration, indicating that the compounds did not pass the blood–brain barrier. The substantial activity of the α-methyl derivatives **12** and **14**, seen upon subcutaneous (sc) administration, indicates that the latter compounds freely cross the blood–brain barrier.

Compounds listed in Table II are functionalized *N*-alkyltroponylpiperazine derivatives. Among these compounds, the *N*-(2-hydroxyethyl) derivative (**35**) showed moderate activity. The pharmacological activity of esters **39** and **40** may be attributable to the alcohol (**35**), which can be generated by in situ hydrolysis. Homologation of alcohol **35** to **41** and the hydroxylation of **41** as in **18** substantially lowered the activity. Etherification of the hydroxy function by an ethyl (**42**) or phenyl (**43**) group also led to loss of activity.

In the functionalized *N*-alkyltroponylpiperazine series, introduction of a methyl group on the carbon atom α to the nitrogen as in **37** led to complete loss of activity. This observation is in contrast to that seen in the alkyl series where a similar change markedly augmented dopamine agonist activity. On the other hand, incorporation of a methyl group β to the nitrogen, as in **36**, substantially increased the cumulative ambulation score. This finding suggests that the alcohol function may be crucial for activity and that any alteration by oxidative metabolism (i.e., $CH_2OH \rightarrow COOH$) may render the compound inactive. A CH_3 group α to the hydroxyl may prevent such oxidative deactivation. This suggestion is also supported by the finding that compounds **44** and **45**, where the carbon has a higher oxidation level, lacked biological activity.

Substitution of the tropone ring markedly influences dopamine agonist activity. Thus, the 5-chloro derivative (**47**) of the alcohol **35** was inactive, whereas the 7-bromo derivative (**48**) was only slightly less active than the parent alcohol.

Compounds **25–28**, described in Table III, are analogues of **8**, whereas compounds **29** and **30** are structurally related to **35**.



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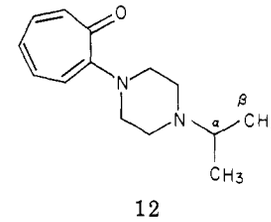

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Replacing either the N-1 or N-4 with a carbon atom in compound **8**, as in **25** and **27**, or homologating the piperazine by an extra methylene group, as in **26**, resulted in the loss of dopamine agonist activity. Replacing the tropone ring of either **8** or **35** by a phenyl nucleus (**28** and **29**) or saturating the tropone ring to cycloheptanone (**30**) also resulted in inactive compounds. The aforementioned changes suggest that both the piperazine and the tropone moieties are necessary to elicit a dopaminergic response.

Experimental Section

The infrared and ultraviolet spectra were recorded on a Perkin-Elmer diffraction grating and Zeiss DMR-21 spectropho-

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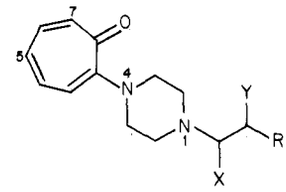
Table II. Effect of Functionalized *N*-Alkyltroponylpiperazines on 6-OHDA-Induced Hypokinesia in Rats



compd	X	Y	R	mp, °C	crystn solv[c]	formula	anal.	dose, mg/kg sc	cumulative ambulation score, means ± SEM
35	H	H	OH	85–86	Ea/H	$C_{13}H_{18}N_2O_2$	C, H, N	50	187 ± 35 (5)[e]
								25	88 ± 23 (5)
36	H	CH_3	OH	92–93	Ea	$C_{14}H_{20}N_2O_2$	C, H, N	50	400 ± 78 (4)
								25	190 ± 67 (5)
37[a]	CH_3	H	OH	115–116	M/E	$C_{14}H_{20}N_2O_2 \cdot C_4H_4O_4$	C, H, N	25	inactive
38	CH_3	CH_3	OH	126	Ea/H	$C_{15}H_{22}N_2O_2$	C, H, N	25	inactive
39	H	H	$OCOCH_3$	oil		$C_{15}H_{20}N_2O_3$	C, H, N	50	232 ± 54 (4)
								25	106 ± 37 (6)
40[a]	H	H	$OCOC(CH_3)_3$	101–102	A/E	$C_{18}H_{26}N_2O_3 \cdot C_4H_4O_4$	C, H, N	50	137 ± 29 (6)
21	H	H	$NHCOCH_3$	117–118	M	$C_{15}H_{21}N_3O_2$	C, H, N	50	inactive
41	H	H	CH_2OH	98–100	Ea/H	$C_{14}H_{20}N_2O_2$	C, H, N	50	71 ± 10 (4)
18	H	OH	CH_2OH	111–112	Ea/H	$C_{14}H_{20}N_2O_3$	C, H, N	50	58 ± 13 (5)
42[a]	H	H	OC_2H_5	137–138	A/E	$C_{15}H_{22}N_2O_2 \cdot C_4H_4O_4$	C, H, N	50	67 ± 16 (7)
43	H	H	OC_6H_5	94–95	Ea/H	$C_{19}H_{22}N_2O_2$	C, H, N	50	inactive
47	H	H	OH (5-Cl)	oil		$C_{13}H_{17}ClN_2O_2$[d]		50	inactive
48[b]	H	H	OH (7-Br)	214–215	Ea/M	$C_{13}H_{17}BrN_2O_2 \cdot HBr$	C, H, N	50	136 ± 31 (6)
44[a]	H	=O	OC_2H_5	106	A/E	$C_{15}H_{20}N_2O_3 \cdot C_4H_4O_4$	C, H, N	50	inactive
45	H	=O	NH_2	169–171	M	$C_{13}H_{17}N_3O_2$	C, H, N	50	inactive
46	H	C≡N		133–135	A/E	$C_{13}H_{15}N_3O$	C, H, N	50	126 ± 51 (6)
bromocriptine								10	112 ± 23 (12)

[a] Maleate salt. [b] Hydrobromide salt. [c] A = acetone; E = ether; Ea = ethyl acetate; H = hexane; M = methanol. [d] This compound was characterized by IR, UV, NMR, and MS. [e] Numbers in parentheses refer to number of rats in each group.

Table III. Effect of Structurally Modified Derivatives on 6-OHDA-Induced Hypokinesia in Rats

compd[a]	mp, °C	crystn solv[d]	formula	anal.	dose, mg/kg sc	cumulative ambulation score, means ± SEM
25[b]	196–197	A	$C_{13}H_{17}NO \cdot C_4H_4O_4$	C, H, N	50	inactive
26[b]	123–124	M/Ea	$C_{13}H_{18}N_2O \cdot C_4H_4O_4$	C, H, N	50	inactive
27	oil		$C_{13}H_{17}NO$	C, H, N	50	inactive
28[c]	142–143	M/E	$C_{11}H_{16}N_2 \cdot HI$[e]	C, H, N	50	inactive
29	78	B	$C_{12}H_{18}N_2O$	C, H, N	50	inactive
30	oil		$C_{13}H_{24}N_2O_2$[e]		50	inactive

[a] For structures, see Scheme IV. [b] Maleate salt. [c] Hydriodide. [d] A = acetone; E = ether; M = methanol; Ea = ethyl acetate; B = benzene. [e] These compounds were characterized by IR, UV, NMR, and MS.

Table IV. Rotational Behavior Induced by Selected Troponylpiperazines in Rats with a Unilateral 6-OHDA-Induced Lesion of the Nigro-striatal Dopamine Pathway

compd	dose, mg/kg sc	total no. of contralateral turns, means ± SEM	duration of act., h
8	75	2842 ± 499 (5)[a]	9
	50	1814 ± 325 (4)	6
	25	551 ± 176 (8)	5
35	75	4582 ± 611 (4)	12
	50	1378 ± 205 (4)	6
	25	369 ± 71 (4)	4
39	75	3640 ± 517 (4)	10
	50	1485 ± 112 (4)	6
	25	743 ± 65 (4)	4
bromocriptine	8	4868 ± 1066 (4)	18

[a] Numbers in parentheses refer to number of rats in each group.

tometer, respectively. The melting points were taken on a Thomas-Hoover apparatus and are uncorrected. The NMR and mass spectra were obtained on a CFT-20 and LKB-9000S spectrometer, respectively. Organic extracts were dried over magnesium sulfate, and the solvents were always removed under vacuum. Merck silica gel 60 (70–230 mesh) was used for column chromatography.

2-(1-Piperazinyl)-2,4-6-cycloheptatrien-1-one. A mixture of 2-methoxytropone (136 g, 1 equiv) and piperazine (136 g, 1.6 equiv) in methanol (250 mL) was refluxed for 4 h.

(a) Acetic Acid Salt (6). The reaction mixture was cooled in ice, diluted with water (150 mL), and acidified with acetic acid. The precipitated ditroponylpiperazine **5** was filtered. The filtrate was evaporated to dryness, and the residue was passed through a column of silica gel, (10 g/g; in chloroform/acetone, 1:1). The remaining ditroponyl compound was eluted with the same solvent, followed by elution of the acetic acid salt with 20% acetic acid in methanol. Removal of the solvent gave oily salt **6** (153 g). The salt gave satisfactory spectral analysis and was used as such for subsequent reactions.

(b) Methanesulfonic Acid Salt (7). The reaction mixture was cooled, and the ditroponylpiperazine was allowed to crystallize out. The filtrate was diluted with acetone to 1 L and then cooled in ice bath, and methanesulfonic acid (106 g) in acetone (250 mL) was added dropwise with stirring. The precipitated salt was filtered to give the product (146 g). A sample showed in its NMR (Me_2SO-d_6) δ 2.35 (3 H, s, CH_3S), 3.35 (8 H, m, CH_2N), 6.95 (5

Table V. Effect of Haloperidol on Dopamine Agonist-Induced Rotation in Unilaterally 6-OHDA-Lesioned Rats

pretreatment[a]	dose, mg/kg ip	no.	dose, mg/kg sc	total no. of turns, means ± SEM	P[b]	% decrease
vehicle		35	75	2413 ± 344		
haloperidol	0.1	35	75	1626 ± 406	ns[c]	−33
	0.25	35	75	1055 ± 294	<0.05	−56
	0.5	35	75	567 ± 202	<0.01	−77

[a] Haloperidol was injected 1 h before the DA agonist. [b] Drug pretreatment vs. vehicle pretreatment; statistical analysis by Student's *t* test. [c] ns, not significant. The same five rats were injected with each treatment regimen.

H, m, olefinic), 8.8 (2 H, br, NH_2^+).

General Procedure for Alkylation of Compound 6 or 7. The alkylation was mostly carried out in acetonitrile in the presence of potassium carbonate at temperatures varying from room temperature to reflux and worked up in the usual manner. A typical procedure is described below:

2-(4-Ethyl-1-piperazinyl)-2,4,6-cycloheptatrien-1-one (9). A mixture of troponylpiperazine acetate (**6**; 7.2 g, 1 equiv), ethyl iodide (3.9 g, 1 equiv), and potassium carbonate (6.9 g, 4 equiv) in acetonitrile (100 mL) was heated to reflux for 16 h. The solvent was removed, and the residue was taken up in water (100 mL) and extracted with chloroform. The extract was dried and evaporated to yield crude product (4 g). A purification by passage through a column of silica gel (250 g) in methanol–ethyl acetate (1:9) and elution with the same solvent yielded the pure title compound (1.9 g).

***N*-[2-[4-(2-Oxo-3,5,7-cycloheptatrien-1-yl)-1-piperazinyl]ethyl]acetamide (21).** A mixture of troponylpiperazine salt **6** (28 g, 1 equiv), *N*-(2-bromoethyl)phthalimide (76.2 g, 3 equiv), and potassium carbonate (27.6 g, 4 equiv) in acetonitrile was refluxed for 16 h. The reaction mixture was cooled and diluted with water (2 L). The organic matter was extracted with chloroform and dried, and the solvent was removed to yield the crude product. Chromatography on silica gel (1.5 kg) gave, upon elution with ethyl acetate, a product (14 g) whose NMR ($CDCl_3$) showed δ 2.7 (6 H, m, CH_2N), 3.3 (4 H, t, CH_2N), 3.85 (2 H, t, CH_2N), 6.8 (5 H, m, troponyl), 7.75 (4 H, m, aromatic). Based on all the spectroscopic data, this compound was assigned structure **19**: mp 124–126; IR ($CHCl_3$) 1705, 1770 cm^{-1}. Further elution with methanol–chloroform (1:1) yielded a compound (6.7 g) whose IR ($CHCl_3$) exhibited no characteristic phthalimide carbonyl; instead it had carbonyl bands at 1630 and 1565 cm^{-1}. In conjunction with its UV, NMR, and MS, it was assigned structure **20**: mp 195–196 °C; NMR ($CDCl_3$) δ 3.3 (6 H, m, CH_2N), 4.12 (6 H, m, CH_2N, CH_2O), 7.2 (9 H, m, aromatic); MS, *m/e* 363 (M^+).

Hydrazinolysis of Compound 19. To a solution of compound **19** (8.7 g, 1 equiv) in ethanol was added hydrazine hydrate (1.3 g, 1.1 equiv). After 24 h at room temperature, the mixture was acidified with 1 N HCl and left to stir at room temperature for 2 h, and the precipitate was filtered. The filtrate was made alkaline with sodium hydroxide (10%) and extracted with choloroform. The organic extract was dried, and the solvent was removed to yield crude product (6 g). The product was filtered with 20% acetic acid–ethyl acetate through a column of silica gel (100 g) and eluted with the same solvent to give pure amine (4 g, 24.3% from **6**).

Acetylation. A mixture of the amine obtained above and acetic anhydride (40 mL) were allowed to react at room temperature for 48 h. The acetic anhydride was removed under vacuum, and the residue was put through a column of silica gel (200 g). Elution with methanol yielded the pure product **21** (1.6 g, 34%): NMR ($CDCl_3$) δ 2.0 (3 H, s, CH_3CO), 2.6 (6 H, m, NCH_2), 3.35 (6 H, m, CH_2N).

2-[4-(2-Aminoethyl)-1-piperazinyl]-2,4,6-cycloheptatrien-1-one (22) Acetate. A mixture of methoxytropone (13.6 g, 1 equiv), 1-(2-aminoethyl)piperazine (12.9 g, 1 equiv), and methanol (100 mL) was refluxed for 3 h. The solvent was evaporated, and the residue was chromatographed on silica gel (250 g) with methanol–acetic acid (8:2). The product was eluted with the same solvent to yield 29 g of the acetate of **22**. Crystallization from ethyl acetate gave pure product (9 g, 30.8%), mp 146–147 °C.

***N*,4-Bis(2-oxo-3,5,7-cycloheptatrien-1-yl)-1-piperazineethanamine (23).** A solution of 2-methoxytropone (4.08 g, 3 equiv) and 1-(2-aminoethyl)piperazine (1.29 g, 1 equiv) in methanol (30 mL) was refluxed for 24 h. The solvent was evaporated, and the residue was chromatographed on silica gel (50 g) with acetic acid–ethyl acetate (1:9). Elution with the same solvent yielded the product (2.4 g). Crystallization from ethyl acetate gave pure **23**: mp 130–132 °C; IR ($CHCl_3$), 3300, 1555 cm^{-1}; NMR ($CDCl_3$) δ 7.6 (1 H, br NH), 6.9 (10 H, m, arom), 3.4 (6 H, m, NCH), 2.8 (6 H, m, NCH).

2-[4-[2-(Acetyloxy)ethyl]-1-piperazinyl]-2,4,6-cycloheptatrien-1-one (24). Quinuclidine hydrochloride (8 g, 1.1 equiv) was neutralized with sodium hydroxide (50%, 5 mL), and the base was extracted in benzene (150 mL). To the benzene solution was added 2-chlorotropone (7.61 g, 1 equiv). The mixture was allowed to react at room temperature for 10 days. The crystalline product that precipitated was filtered and washed with benzene to yield **1-(2-oxo-3,5,7-cycloheptatrien-1-yl)quinuclidinium chloride** (6.13 g, 45%): NMR δ 2.2 (6 H, m, CCH_2), 2.7 (2 H, s, NCH_2), 3.7 (1 H, m, >CH), 4.3 (4 H, t, N-CH_2), 7.5 (4 H, m, arom), 8.9 (1 H, d, arom). The above salt was refluxed in ethanol (60 mL) for 16 h. The solvent was evaporated to dryness, and the residue was put on silica gel (400 g) with ethyl acetate–hexane (3:7) and eluted with the same solvent to yield (0.853 g, 14%) pure product, mp 97–98 °C. This material was suspended in dry acetonitrile (40 mL) and potassium acetate (1 g), and 18-crown ether-6 (0.15 g) was added to it. The mixture was refluxed for 30 h. The solvent was removed, and the residue was chromatographed on silica gel (100 g) in ethyl acetate–hexane (4:6) to yield pure product (oil, 0.82 g, 75%): NMR ($CDCl_3$) δ 1.6 (7 H, m, CCH_2, >CH), 2.01 (3 H, s, $OCOCH_3$), 2.73 (2 H, t, NCH_2), 3.85 (2 H, t, NCH_2), 4.09 (2 H, t, CH_2OCO), 6.4–7.1 (5 H, m, arom); IR ($CHCl_3$) 1725, 1560 cm^{-1}; UV (MeOH) λ_{max} 356 nm (ε 8180), 258 (12450), 222 (10465).

2-(1-Methyl-4-piperidinyl)-2,4,6-cycloheptatrien-1-one (*Z*)-2-Butenedioate (25). The reaction was carried out under an atmosphere of dry nitrogen. Magnesium (2.4 g) was covered with dry tetrahydrofuran (10 mL). A crystal of iodine was added, followed by ethyl bromide (0.535 g). After the reaction had subsided, a solution of 4-chloro-1-methylpiperidine (13.1 g, obtained by neutralization of the HCl salt, 20 g) in tetrahydrofuran (35 mL) was added at a rate maintaining gentle reflux. After the addition was over, the mixture was refluxed for 1 h and cooled in ice bath, and 2-methoxytropone (6.8 g) was gradually added. The mixture was stirred and allowed to reach room temperature. Ammonium chloride (saturated solution) was added, and the mixture was extracted with methylene chloride to yield, after evaporation of the solvent, a crude residue (10 g). The residue was partitioned between water–chloroform to yield the organic matter (4.3 g). After two passages through silica gel and elution with ammonium hydroxide–methanol (2:98), pure base (0.33 g) was obtained. The maleate salt was prepared by dissolving the base (0.15 g) in acetone (2 mL) and adding maleic acid (1.1 equiv). The resulting precipitate was stirred for 4 h and filtered to yield (0.17 g, 1.2%) the salt of the title compound: NMR (Me_2SO-d_6) δ 1.95 (4 H, m, CCH_2), 2.80 (3 H, s, NCH_3), 3.35 (5 H, m, NCH_2, CH), 6.00 (2 H, s, C=CH), 7.75 (5 H, m, arom), IR (Nujol) 2500, 1675, 1580, 1360 cm^{-1}; UV (MeOH) λ_{max} 243 nm (ε 15025).

2-[4-(2-Hydroxyethyl)-1-piperazinyl]-1-cycloheptanone (30). A solution of 4-(2-oxo-3,5,7-cycloheptatrien-1-yl)-1-piperazineethanol (5 g) in methanol (100 mL) was hydrogenated in the presence of 10% Pd/C (1 g) at 50 psi for 8 h. The catalyst was filtered, and the solvent was evaporated. The residue (5 g) was converted to its hydrochloride salt and crystallized twice from methanol–ether, and the regenerated base was chromatographed on silica gel (50 g) to yield, on elution with methanol–ethyl acetate (4:6), pure product (0.65 g, 13%): NMR ($CDCl_3$) δ 1.7 (8 H, m,

CCH_2), 2.5 (10 H, m, NCH_2), 3.0 (1 H, N >CH), 3.56 (2 H, t, CH_2O); IR ($CHCl_3$), 3660, 3440, 1697 cm^{-1}.

Pharmacology Methods. Animals. Experiments were performed on male Sprague–Dawley rats housed in air-conditioned quarters. The room was lighted between 0700 and 1900 h daily and was maintained at a temperature of 24 ± 2 °C.

Materials. In addition to the test compounds, the following drugs were used: 6-hydroxydopamine hydrobromide (Aldrich Chemical Co., Inc.) and bromocriptine methanesulfonate (generous gift of Sandoz Pharmaceuticals). The doses used were calculated as the free base. The compounds were dissolved in distilled water or suspended in distilled water with a few drops of Tween 80 (2–3 drops/10 mL). Fresh solutions were prepared on the day of the experiment.

6-OHDA-Induced Hypokinesia in Rats. Details of the lesioning procedure and behavioral testing were recently described.[16] Briefly, the rats (approximately 280 g) were anesthetized with sodium pentobarbital and placed in a Stoelting stereotaxic instrument. 6-OHDA (26 μg/4 μL) was injected bilaterally into the anterolateral hypothalamus[14] by using the DeGroot[28] brain atlas. Four days postoperatively, the rats were placed into an open field, the floor of which was divided into 36 squares (11.5 × 11.5 cm). The rats were observed for a 2-min period, and only rats with almost total akinesia were used. Drug effect was evaluated in the course of six 2-min test periods, 15, 30, 45, 60, 90, and 120 min after the sc administration of the troponylpiperazines and 2, 3, 4, 5, 6, and 7 h after the sc administration of bromocriptine. The placement of all four limbs in one square was taken as one ambulation score. The results are expressed as cumulative ambulation scores, which are the sums of the scores obtained during the 2-min observation periods.

Rotational Behavior in Unilaterally 6-OHDA-Lesioned Rats. The body weights of the rats were approximately 250 g at the time of the stereotaxic operation. During the course of the subsequent rotational experiments, the rats were housed individually and received about 20 g of food per day, which maintained their body weight between 350 and 400 g.

The lesioning procedure was based upon the method of Ungerstedt[19] utilizing the modifications of Pycock and Marsden.[29] The rats were anesthetized with sodium pentobarbital, 40 mg/kg ip, and immobilized in a Stoelting stereotaxic instrument. Unilateral injections of 6-OHDA (8 μg in 3 μL delivered at a rate of 1 μL/min) were made into the left ascending median forebrain bundle (MFB) in the lateral hypothalamus using the stereotaxic coordinates of the DeGroot[28] brain atlas (A, +4.6; L, 1.9; V, −2.7). 6-OHDA was made up in distilled water containing 0.2 μg/μL of ascorbic acid and kept in ice throughout the injection procedure.

Three to four weeks after lesioning, the rats were tested for rotational behavior in response to apomorphine, 0.25 mg/kg sc. Rats that turned 8–10 times per minute during peak activity were selected for further drug trials.

Rotational behavior was determined in automatically recording rotometers, details of which were recently described.[30] Groups of four to eight rats were injected sc with the test compounds and then placed immediately into the rotometer. Rotational behavior was continuously recorded until its cessation. The results are expressed as total number of turns.

Acknowledgment. The authors express their appreciation to Dr. G. Shilling and his associates for microanalytical and spectral data. The skillful assistance of M. Asselin and J. Csakvary in the chemical synthesis and N. Lapeyre and Ida Vozzella in the pharmacological studies is gratefully acknowledged.

Registry No. **4**, 80100-68-1; **5**, 80100-67-0; **6**, 89746-93-0; **7**, 80100-70-5; **8**, 80100-56-7; **8** maleate, 89746-94-1; **9**, 80100-76-1; **10**, 80100-77-2; **11**, 89746-95-2; **11**·HCl, 80100-82-9; **12**, 80100-75-0; **13**, 80100-61-4; **13** maleate, 80100-62-5; **14**, 89746-96-3; **14** maleate, 89746-97-4; **18**, 80100-90-9; **19**, 80100-83-0; **19** (amine derivative), 80100-88-5; **20**, 80100-84-1; **21**, 80100-89-6; **22**·HOAc, 89746-99-6; **23**, 80100-95-4; **24**, 89747-00-2; **25**, 89747-01-3; **25** maleate, 89747-02-4; **26**, 89747-03-5; **26** maleate, 89747-04-6; **27**, 89747-05-7; **28**, 3074-43-9; **28**·HI, 89747-06-8; **29**, 36245-26-8; **30**, 89747-07-9; **35**, 80101-15-1; **36**, 80101-56-0; **37**, 80101-27-5; **37** maleate, 80101-28-6; **38**, 80101-41-3; **39**, 80101-16-2; **40**, 80101-17-3; **40** maleate, 80101-18-4; **41**, 80101-24-2; **42**, 80101-01-5; **42** maleate, 80101-02-6; **43**, 80101-00-4; **44**, 80100-98-7; **44** maleate, 80100-99-8; **45**, 80101-14-0; **46**, 80100-96-5; **47**, 80101-22-0; **48**, 89747-08-0; **48**·HBr, 80101-23-1; 2-methoxytropone, 2161-40-2; 2-chlorotropone, 3839-48-3; piperazine, 110-85-0; 1-(2-aminoethyl)piperazine, 140-31-8; 1-*tert*-butylpiperazine, 38216-72-7; *N*-(2-bromoethyl)-phthalimide, 574-98-1; quinuclidine hydrochloride, 39896-06-5; 1-(2-oxo-3,5,7-cycloheptatrien-1-yl)quinuclidinium chloride, 89747-09-1; 4-chloro-1-methylpiperidine, 5570-77-4.

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Sulfur Analogues of Psychotomimetic Agents. 3. Ethyl Homologues of Mescaline and Their Monothio Analogues†

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All possible monothio analogues of the mono-, di-, and triethoxy homologues of mescaline have been synthesized and pharmacologically evaluated in man. Modifications at the ring position para to the ethylamine chain, either with a sulfur atom, a longer alkyl chain, or both, lead to compounds of high central nervous system activity. The 4-*n*-propoxy and 4-*n*-butoxy homologues and their corresponding 4-thio analogues were also synthesized and pharmacologically evaluated. The propyl homologues retain high potency, but a butyl group (either with or without a sulfur atom) leads to a decrease in activity. The *m*-ethyl or *m*-thio analogues retain some central action but the diethoxy and especially the triethoxy homologues are relatively inactive as psychotomimetic drugs.

Although, mescaline (**1a**) has rather low psychotomimetic potency, its simple structure, together with its complex and well-characterized psychological intoxication profile, has made it a desirable paradigm for structure–activity relationship inquiries.

Human clinical studies of homologues of **1a** (Chart I) have centered on three structural positions: (a) alkylation of the primary amine function, (b) alkylation of the position α to this amine group, or (c) homologation of the *p*-methoxy group. *N,N*-Dimethylmescaline (Trichocerine) is reported to be of reduced potency, showing little, if any central activity even at twice the effective dosage of **1a**.[1]

† For paper 2 in this series, see ref 24.
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0022-2623/84/1827-0881$01.50/0