detected at 220 nm, and the eluate was collected in 5-mL fractions. Tubes comprising the product were pooled, the organic solvent was evaporated, and the aqueous phase was lyophilized to give 58 mg of title compound. HPLC as for **3** showed a single sharp peak. Amino acid analysis: Pro, 2.03; Ile, 0.79; Phe, 3.0; His, 3.06; Lys, 1.04.

Plasma Renin Inhibitory Activity Testing. Lyophlized human plasma with 0.1% EDTA was obtained commercially (New England Nuclear). The angiotensin I generation step utilized 250 μL of plasma, 2.5 μL of phenylmethylsulfonyl fluoride, 25 μL of maleate buffer (pH 6.0), and 10 μL of an appropriate concentration of inhibitor in a 1% Tween 80 in water vehicle. Incubation was for 90 min at 37 °C. Radioimmunoassay for angiotensin I was carried out with a commercial kit (Clinical Assays). Plasma renin activity values for inhibitor tubes were compared to control tubes to estimate percent inhibition. The inhibition results were expressed as IC_{50} values, which were obtained by plotting three to four inhibitor concentrations on semilog graph paper and estimating the concentration producing 50% inhibition. Details of the assay are given in ref 27.

Acknowledgment. We gratefully acknowledge G. Skala for synthetic assistance, J. Nielsen and L. Baczynskyj for FAB mass spectroscopy, P. A. Meulman for IR spectroscopy, and P. Lupina for excellent secretarial work.

Registry No. **1**, 95190-14-0; **2**, 103436-26-6; **3**, 114423-48-2; **4**, 103477-15-2; **5**, 114423-49-3; **6**, 114443-30-0; **7**, 114489-13-3; BOC-Dhs-OMe, 114423-50-6; BOC-(*Z*)-Dhs-OMe, 114423-51-7; BOC-Dhs-OH, 101670-81-9; BOC-D-Lys(Cl-Z)-OH, 57096-11-4; BOC-His(Tos)-OH, 35899-43-5; BOC-Ile-OH, 13139-16-7; BOC-His(Tos)-OH·DCHA, 65057-34-3; BOC-Phe-OH, 13734-34-4; BOC-Pro-OH, 15761-39-4; BOC-Leuψ[CH_2S]Val-OH, 114443-31-1; BOC-Sta-OH, 58521-49-6; H-Val-OBzl, 21760-98-5; BOC-Leuψ-[CH_2NH]Val-OBzl, 82252-38-8; BOC-Leuψ[CH_2NH]Val-OH, 82252-39-9; Ph_3P=CHCOOMe, 2605-67-6; (*S*)-HOOCCH(SH)-$CHMe_2$, 114423-53-9; BOC-leucinol, 82010-31-9; BOC-leucinal, 58521-45-2; 4-[(*tert*-butyloxycarbonyl)amino]-4-hydroxy-6-methylheptanoic acid lactone, 114423-52-8; (2*S*)-2-[(*tert*-butyloxycarbonyl)amino]-1-[(*p*-tolylsulfonyl)oxy]-4-methylpentane, 112157-30-9; renin, 9015-94-5.

Polycyclic Aryl- and Heteroarylpiperazinyl Imides as 5-HT_{1A} Receptor Ligands and Potential Anxiolytic Agents: Synthesis and Structure–Activity Relationship Studies

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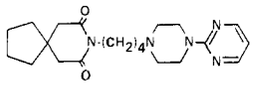
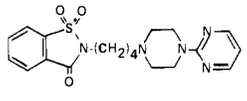
A series of polycyclic aryl- and heteroarylpiperazinyl imides were prepared and tested in various receptor-binding and behavioral tests. Parameters measured included in vitro inhibition of D_2 and 5-HT_{1A} receptor binding, inhibition of apomorphine (APO) induced stereotyped and climbing behavior, and activity in blocking conditioned avoidance responding (CAR). Several compounds demonstrated moderate to high affinity for the 5-HT_{1A} receptor binding site; compounds **27** and **36** containing the serotonin mimetic (*o*-methoxyphenyl)piperazinyl moiety and compounds **42** and **50** containing the 2-pyrimidinylpiperazinyl moiety displayed the highest affinity, being equal to that of the 5-HT_{1A} agonist 8-OH-DPAT (K_i = 1–1.3 nM). In addition to affinity at 5-HT_{1A} binding sites, many compounds were active in blocking CAR. Compound **34**, 2-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]hexahydro-4,7-etheno-1*H*-cyclobut[*f*]isoindole-1,3(2*H*)-dione, demonstrated 3 times the activity of buspirone, blocking CAR in rats with an AB_{50} of 13 mg/kg. It also displayed high affinity for the 5-HT_{1A} receptor (K_i = 16 nM), which is at least 20 times higher than its affinity for D_2 (K_i = 345 nM) and 5-HT_2 (K_i = 458 nM) receptors. Compound **34** was selected for further preclinical and pharmacokinetic evaluations for possible development as an anxiolytic agent. Structure–activity relationships within this series are discussed.

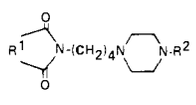
In the last decade serotonin (5-HT) has been implicated in anxiety, depression, insomnia, and other behavioral disorders.[1-3] Multiple subtypes of 5-HT_1 receptors have been recently identified with radioligand binding assays which include 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1C} receptor subtypes.[4] In recent years, a growing body of literature has attributed the activity of the non-benzodiazepine anxiolytic agents buspirone (**1**) and ipsapirone (**2**) to their selective activation of the 5-HT_{1A} receptor.[5-7] 5-HT_{1A} receptors are found predominantly in the hippocampus and dorsal raphe nucleus[4] and are sensitive to spiperone and 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT).[8] Preclinical evidence for a 5-HT_{1A} receptor mediated mechanism of anxiolysis of non-benzodiazepine drugs such as **1** and **2** has been provided mainly through in vitro and in vivo radioligand binding assays.[6]



1



2



3

The launch of buspirone (**1**) has created much interest in alternative, non-benzodiazepine treatment of anxiety, and consequently, synthetic efforts have been devoted by us and others in an attempt to develop potent ligands with high affinity and selectivity for the 5-HT_{1A} receptor subtype.

(1) Johnston, A. L.; File, S. E. *Pharmacol. Biochem. Behav.* **1986**, *24*, 1467.
(2) Eison, M. S. *Psychopathology* **1984**, *17*, 37.
(3) Peroutka, S. J.; Snyder, S. H. *Pharmacol. Exp. Ther.* **1981**, *216*, 142.
(4) Pazos, A.; Palacios, J. M. *Brain Res.* **1985**, *346*, 205.
(5) Eison, A. S.; Eison, M. S.; Stanley, M.; Riblet, L. *Pharmacol. Biochem. Behav.* **1986**, *24*, 701.
(6) Spencer, D. G., Jr.; Traber, J. *Psychopharmacology* **1987**, *91*, 25.
(7) Dompert, W. U.; Glaser, T.; Traber, J. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1985**, *328*, 467.
(8) Middlemiss, D. N.; Sozard, J. R. *Eur. J. Pharmacol.* **1983**, *90*, 151.

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Scheme I

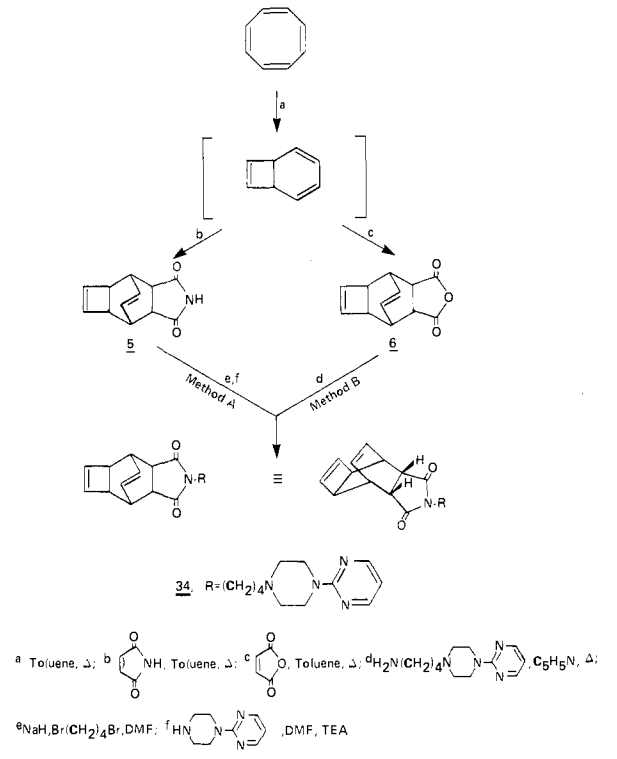
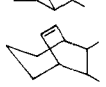
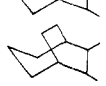
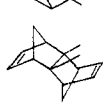


Table I. Polycyclic Imides and 1,2-Dicarboxylic Anhydrides

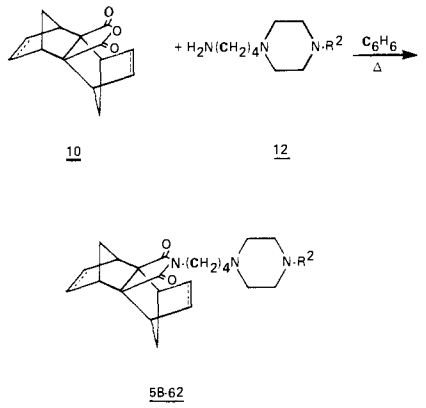
Compound	R^1	X	mp, °C	% Yield	Formula	Ref
4		NH	238-239	79	$C_{11}H_{11}NO_2$	10
5		NH	258-260	78	$C_{11}H_{11}NO_2$	10
6		O	165-167	85	$C_{11}H_{10}O_3$	9
7		NH	196-198	70	$C_{11}H_{13}NO_2$	-
8		NH	145-147	85	$C_{11}H_{15}NO_2$	-
9		NH	200-202	54	$C_{12}H_{14}NO_2$	-
10		O	230-234	68	$C_{16}H_{12}O_3$	12
11		NH	320-322	55	$C_8H_9NSO_4$	11

In this paper we report the synthesis, behavioral activity, and receptor-binding profile of a series of polycyclic aryl- and heteroarylpiperazinyl imides **3**.

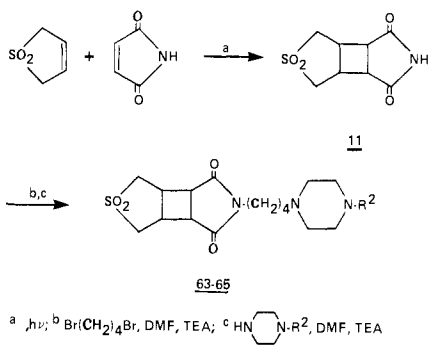
Chemistry

Literature procedures[9-11] were adopted for the synthesis of unsubstituted polycyclic imides and polycyclic dicarboxylic acid anhydrides. As shown in Scheme I, key intermediates can be prepared by reacting maleimide or maleic anhydride with the appropriate diene; for example, the reaction 1,3,5,7-cyclooctatetraene with maleimide or maleic anhydride afforded hexahydro-4,7-etheno-1*H*-cyclobut[*f*]isoindole-1,3(2*H*)-dione (**5**) or its dicarboxylic acid anhydride (**6**) in 78% and 85% yields, respectively. Similarly, intermediates **7**–**9** (Table I) were prepared via Diels–Alder reaction of maleimide with 1,3-cycloheptadiene or 1,3-cyclooctadiene in 70% and 54% yields, respectively. In contrast, anhydride **10** was prepared in 68% yield via the Diels–Alder reaction of norbornadiene-2,3-dicarboxylic anhydride with cyclopentadiene following Edman's procedure.[12] Saturated derivatives of polycyclic imides and anhydrides were prepared by hydrogenating the unsaturated compounds with hydrogen and Pd/C as a catalyst. Alternatively, Scheme III illustrates the synthesis of tetrahydrothienocyclobutapyrroledione 2,2-dioxide (**11**) in which an equimolar solution of sulfolene and maleimide in acetone was photolyzed with a Hanovia 450-W type L mercury lamp while the solution was stirred for 4 h.

Scheme II



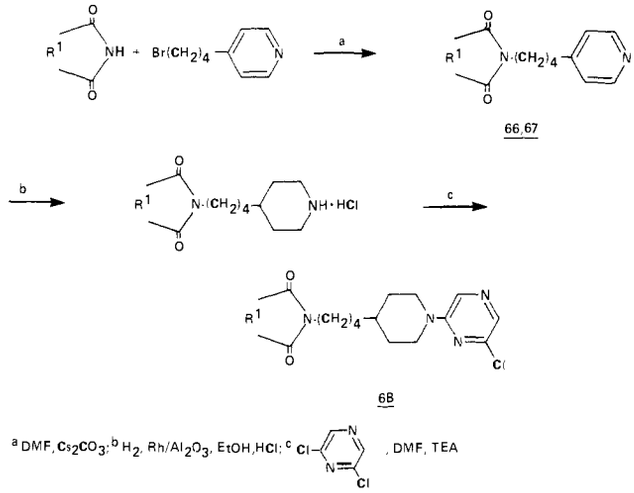
Scheme III



Two general synthetic procedures were utilized in preparing the desired polycyclic heteroarylpiperazinyl imides **13**–**68**, which are exemplified in the synthesis of **34** as shown in Scheme I. Aryl- or heteroarylpiperazines were either directly reacted with polycyclic haloalkyl imides (Schemes I and III), which were generated from the reaction of the corresponding imides **4**, **5**, **7**, **9**, and **11** with dihaloalkane, or converted first to (aminoalkyl)piperazines, followed by a reaction with the appropriate anhydrides **6** and **10** (Schemes I and II). Butylamines **12** were prepared following a modified procedure of Wu et al.[13] in which the appropriately substituted arylpiperazines or heteroarylpiperazines were reacted with 4-bromobutyronitrile in DMF in the presence of triethylamine to afford the corresponding nitrile derivatives. Catalytic hydrogenation of

(9) Shepard, K. L.; Paleveda, W. J., Jr. U.S. Patent 4 006 233, 1977.
(10) Arya, V. P.; Shenoy, S. J. *Indian J. Chem., Sect. B.* **1976**, *14*, 780.
(11) Shaikhrazieva, V. Sh.; Enikeev, R. S.; Tolstikov, G. A. *J. Org. Chem. USSR (Engl. Transl.)* **1972**, 377.
(12) Edman, J. R.; Simmons, H. E. *J. Org. Chem.* **1968**, *33*, 3808.
(13) Wu, Y-H.; Rayburn, J. W. *J. Med. Chem.* **1972**, *15*, 477.

Scheme IV



the nitrile derivative in the presence of 5% Rh/Al_2O_3 afforded the corresponding butylamine derivative in 40–70% yields, and they were used without further purification.

In an attempt to study the effect of replacing the piperazinyl moiety with a piperidinyl functionality, imide **4** was reacted with 4-pyridinylbutyl bromide hydrobromide[14] in DMF in the presence of cesium carbonate to afford the corresponding butylpyridinyl imide **66** in 62% yield. Hydrogenation of **66** in ethanol in the presence of 5% Rh/Al_2O_3 followed by alkylation with 2,6-dichloropyrazine afforded the desired product **68** in 43% overall yield as shown in Scheme IV.

Biological Results and Discussions

The affinity of these compounds for central dopamine-2 (D_2) and 5-HT_{1A} neuroreceptors in vitro was assessed by their abilities to displace [^{3}H]spiperone and [^{3}H]-8-OH-DPAT, respectively. D_2 binding was assessed in rat brain limbic tissue, whereas 5-HT_{1A} binding was measured in hippocampal tissue (see the Experimental Section).

While the 5-HT_{1A} binding of these compounds is indicative of possible anxiolytic activity, such data are not conclusive. In behavioral tests, compounds were examined in mice for their ability to block various effects of apomorphine (i.e. stereotyped and climbing behavior). Reduction of avoidance responding in conditioned avoidance tests is known to correlate with non-benzodiazepine (buspirone-like) anxiolytic activity as well as preclinical antipsychotic activity.[15,16] Consequently, the abilities of compounds to block the response of rats trained to avoid electrical shock in shelf-jump and/or discrete trial conditioned avoidance procedures after ip and/or oral administration was measured. Although the inhibition of conditioned avoidance responding is evidence of general tranquilizing properties rather than anxiolytic activity, per se, buspirone and related analogues have been shown to inhibit CAR.[15] Insofar as CAR inhibition may also be correlated with preclinical antipsychotic activity,[16] the abilities of compounds to block the response of rats trained to avoid electrical shock in shelf-jump and/or discrete trial conditioned-avoidance procedures after ip and/or oral administration were evaluated as measures of in vivo CNS effects.

Compounds were considered to be inactive if ED_{50} values were greater than 60 mg/kg in the APO-induced stereotyped behavior test (high dose procedure reported earlier)[17] and if the AB_{50} values were greater than 40 mg/kg in the CAR paradigm. Biological data for all synthesized compounds and reference compounds buspirone and ipsapirone are shown in Tables II–V.[18]

Structure–Activity Relationships

Polycycloalkyl Modification. Several compounds demonstrated moderate to high affinity for the 5-HT_{1A} receptor binding site. In general, increasing the lipophilicity of the aryl- and heteroarylpiperazinyl imides by saturation and/or annelation of the cycloalkyl moiety increased their affinity for the 5-HT_{1A} binding site. Effect of lipophilicity expressed as octanol–water partition coefficient[19] (log *P*) and 5-HT_{1A} receptor affinity is shown in Table VI. Replacing the cyclopropyl ring in compound **21** with a cyclobutenyl ring (as in compound **33**) increases lipophilicity and consequently increases the affinity for the 5-HT_{1A} binding site (K_i = 38 and 17 nM, respectively). Saturation of the ethylene bridge in **21** yielded compound **29**, which demonstrated 5-HT_{1A} affinity 3 times higher than **21** (K_i = 14 and 38 nM, respectively). Furthermore, partial saturation and full saturation of the two double bonds in compound **34** afforded more lipophilic compounds **42** and **50**, which demonstrated higher affinity for the 5-HT_{1A} receptor site. Their receptor affinity was equal to that of the 5-HT_{1A} agonist 8-OH DPAT (K_i values of 1.3 and 1 nM, respectively).

Heteroarylpiperazinyl Variants. In general, compounds containing a pyrimidinylpiperazinyl moiety demonstrated the highest activity in displacing both D_2 and 5-HT_{1A} receptor radioligands. In contrast, compounds with (chloropyrazinyl)piperazinyl, chlorodiazinyl, and *N*-methyltetrazolyl moieties showed the weakest activity at these sites. For example, replacing the pyrimidinyl group in **42** with a 6-chloropyrazinyl moiety yielded compound **43** in which both D_2 and 5-HT_{1A} receptor affinities were drastically decreased. D_2 affinity decreased from 85 nM in **42** to 413 nM in **43**, and 5-HT_{1A} affinity decreased from 1.3 nM in **42** to 190 nM in **43**. Compounds with a 2-pyrazinyl moiety, such as **45**, demonstrated moderate activity at both D_2 and 5-HT_{1A} receptor binding sites.

During the course of our study it became apparent that the incorporation of 6-chloropyrazinyl moiety into the polycyclic imide skeleton induced or enhanced oral activity in the CAR test. Compounds **21**, **52**, and **63**, containing the 2-pyrimidinyl moiety, were orally inactive and oral activity was induced in compounds **22**, **53**, and **64** via replacement of the 2-pyrimidinyl moiety with 6-chloropyrazinyl moiety. In contrast, compound **34**, containing the 2-pyrimidinyl moiety, was the most potent compound, blocking CAR with an AB_{50} of 13 mg/kg (3 times the potency of buspirone).

Arylpiperazinyl Variants. Incorporation of the serotonin mimetic substituted phenylpiperazinyl moieties, such as the (*m*-chlorophenyl)piperazinyl, (*o*-methoxyphenyl)piperazinyl, and [*m*-(trifluoromethyl)phenyl]-

(14) Mioque, M.; Gautier, J. A. C. R. *Hebd. Seances Acad. Sci.* **1961**, *252*, 2416.
(15) Yevich, J. P.; Temple, D. L., Jr.; New, J. S.; Taylor, D. P.; Riblet, L. A. *J. Med. Chem.* **1983**, *26*, 194.
(16) Fielding, S.; Lal, H. *Handbook of Psychopharmacology*; Iversen, L. L., Iversen, S. D., Snyder, S. H., Eds.; Plenum: New York, 1978; Vol. 10, p 91.
(17) Abou-Gharbia, M.; Patel, U.; Moyer, J. M.; Muth, E. A. *J. Med. Chem.* **1987**, *30*, 1100.
(18) After the completion of our work, Summitomo Chemical Co. reported on the synthesis of compounds **13**, **14**, and **18** in U.S. Patent 4 507 303, 1985. No 5-HT_{1A} receptor binding data or CAR activity was reported.
(19) McCall, J. M. *J. Med. Chem.* **1975**, *6*, 549.

piperazinyl groups, into the polycyclic imide skeleton resulted in an enhancement of affinity of most of these compounds for D_2 and 5-HT_{1A} receptor sites with little or no change in potency to inhibit CAR. However, compound **35** demonstrated high affinity for 5-HT_{1A} receptor sites (K_i = 41 nM) and lacked affinity at D_2 receptor sites.

Incorporation of Sulfonyl Group into Cycloalkyl Moiety. This resulted in compounds with diminished in vitro binding activity. Tetrahydrothienocyclo imides **63–65** (Table IV) containing the cycloalkylsulfonyl moiety demonstrated weak affinity for D_2 receptors and were inactive at the 5-HT_{1A} receptor sites regardless of the heteroaryl substituent on the piperazine moiety.

Piperazinyl Group Modification. Replacement of the heteroarylpiperazinyl moiety with the heteroarylpiperidinyl functionality resulted in compounds such as **68**. These compounds showed diminished activity at D_2 and 5-HT_{1A} binding sites and also diminished potency to inhibit CAR.

Apomorphine-Induced Stereotyped and Climbing Behavior. Polycyclic imides **13–68** were tested in preclinical animal tests designed to assess the potential of these compounds to produce extrapyramidal side effects (EPS). All compounds failed to antagonize high-dose APO-induced stereotyped behavior at doses up to 60 mg/kg ip, except for compounds **24, 27, 34, 36,** and **45** (Table VII). Of these compounds, **34** was found to inhibit APO-induced climbing (ED_{50} = 3 mg/kg) much more potently than stereotyped behavior (ED_{50} = 23 mg/kg). As climbing behavior induced by apomorphine is more closely related with mesolimbic dopaminergic function, as opposed to striatal function,[20] this result suggests a low potential for extrapyramidal side effects for compound **34**.

In conclusion, several polycyclic aryl- and heteroarylpiperazinyl imides demonstrating high affinity for 5-HT_{1A} receptor binding sites were synthesized. One of these compounds, **34** (Wy-47,846), shares with buspirone a similar favorable neurochemical profile (high 5-HT_{1A} and low D_2 receptor affinities) and was potent in blocking CAR. It was selected for further preclinical and pharmacokinetic evaluation as a possible anxiolytic agent.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Spectra were recorded for all compounds and were consistent with assigned structures. NMR spectra were recorded on Varian XL-300 and XL-100 instruments. Mass spectra were recorded with a Kratos MS-25 mass spectrometer. IR spectra were recorded with a Perkin-Elmer 299 infrared spectrophotometer. Elemental analyses were performed with a Perkin-Elmer Model 240 elemental analyzer by the analytical section of our laboratories and analyses were within ±0.4% of the theoretical values.

4,5,6,7,8,8a-Hexahydro-4,8-ethenocyclohepta[*c*]pyrrole-1,3(2*H*,3a*H*)-dione (7). To a solution of 1,3-cycloheptadiene (4.7 g, 0.05 mol) in dry xylene (75 mL) was added maleimide (4.8 g, 0.05 mol) and the mixture was refluxed for 3 h. On cooling, a white solid was separated, which was filtered and recrystallized from a chloroform–methanol (1:1) mixture to afford 6.7 g (70% yield) of **7**; mp 196–198 °C. Anal. ($C_{11}H_{13}NO_2$).

3a,4,4a,5,6,6a,7,7a-Octahydro-4,9-etheno-1*H*-cycloocta[*c*]pyrrole-1,3(2*H*)-dione (9) was prepared similarly to **7** in 54% yield by refluxing equimolar amounts of 1,3-cyclooctadiene and maleimide in 1,2-dichloroethane for 1 h; mp 200–202 °C. Anal. ($C_{12}H_{14}NO_2$).

Tetrahydro-1*H*-thieno[3′,4′:3,4]cyclobuta[1,2-*c*]pyrrole-4,6(3*H*,5*H*)-dione 2,2-Dioxide (11). A clear solution of sulfolene (5.9 g, 0.05 mol) and maleimide (4.7 g, 0.05 mol) in acetone was photolyzed with a Hanovia 450-W type L mercury lamp while the solution was cooled and stirred under N_2 for 2 h. The separated solid was filtered and recrystallized from ethylacetate to afford 8 g (74% yield) of **11**; mp 320–322 °C (lit.[9] mp 345 °C). Anal. ($C_8H_9NSO_4$).

General Procedure for the Synthesis of Compounds Listed in Table II. 2-[4-[4-(2-Pyrimidinyl)-1-piperazinyl]butyl]-hexahydro-4,7-etheno-1*H*-cyclobut[*f*]isoindole-1,3(2*H*)-dione (34). Method A. To a stirred solution of 3a,4,4a,6a,7,7a-hexahydro-4,7-etheno-1*H*-cyclobut[*f*]isoindole-1,3(2*H*)-dione (**5**) (7.0 g, 0.035 mol) in 70 mL of DMF was added 0.9 g of NaH. The suspension was stirred at 60 °C for 0.5 h and was poured into a stirred solution of 1,4-dibromobutane (9 g, 0.04 mol) in 50 mL of DMF. The reaction mixture was stirred at room temperature overnight, the solvent was removed under vacuum, and the solid cake was suspended in water and extracted with methylene chloride (3 × 300 mL). The methylene chloride extracts were collected, washed with water, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was solidified to a waxy material, affording 8 g (68% yield) of the corresponding 2-(4-bromobutyl)hexahydro-4,7-etheno-1*H*-cyclobut[*f*]isoindole-1,3(2*H*)-dione. To a stirred solution of the above bromobutyl intermediate (2.3 g, 0.07 mol) in 50 mL of DMF were added triethylamine (6 mL) and 1-(2-pyrimidinyl)piperazine dihydrochloride (3.4 g, 0.007 mol). The reaction mixture was stirred at room temperature for 24 h and DMF was removed under reduced pressure. The remaining semisolid was extracted with 2 × 100 mL of methylene chloride, and the methylene chloride extracts were dried over anhydrous Na_2SO_4 and evaporated under vacuum. It afforded a crude product, which was recrystallized from an ethanol–ethyl acetate (1:2) mixture to give 2 g (68% yield) of **34** as the pure free base; mp 168–170 °C, which was converted to the hydrochloride salt; mp 254–256 °C. Anal. ($C_{24}H_{29}N_5O_2$·HCl).

Method B. A mixture of an equimolar quantity of 3a,4,4a,6a,7,7a-hexahydro-4,7-ethenocyclobut[*f*]isobenzofuran-1,3-dione (**6**) and 1-(4-aminobutyl)-4-(2-pyrimidinyl)piperazine in pyridine was refluxed overnight. Pyridine was removed under reduced pressure and the resulting solid was recrystallized from ethanol–ethyl acetate (1:2) mixture to afford **34** as a white solid, mp 167–169 °C, which was converted to the hydrochloride salt; mp 256–258 °C.

Compounds 13–57 in Table II were prepared similarly by reacting the appropriate polycyclic diacid anhydride with the appropriately substituted (aryl- or heteroarylpiperazinyl)butanamine (**12**) as described for **34** (method B). In the event that butylamines **12** are not easily accessible, the desired compounds can be prepared by method A via the reaction of polycyclic halobutyl imides with the appropriate aryl- or heteroarylpiperazines.

General Procedure for the Preparation of Compounds of Table III. 1,4,5,8-Tetrahydro-10-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-4a,8a-(methaniminomethano)-1,4:5,8-dimethanonaphthalene-9,11-dione (59). A mixture of 1,4,4a,5,8,8a-hexahydro-1,4:5,8-dimethanonaphthalene-4a,8a-dicarboxylic anhydride (**10**) (4.5 g, 0.02 mol) and 1-(4-aminobutyl)-4-(2-pyrimidinyl)piperazine (4.8 g, 0.02 mol) in 50 mL of dry pyridine was refluxed overnight. The pyridine was removed under reduced pressure and the remaining oil was subjected to preparative HPLC using a silica gel column and ethyl acetate as the eluent. The title compound was separated and converted to the hydrochloride salt; mp 165–166 °C. Anal. ($C_{26}H_{31}N_5O_2$·2HCL).

Compounds 58, 60, 61, and 62 in Table III were similarly prepared from this corresponding dicarboxylic acid anhydride and appropriate heteroarylpiperazinylbutanamine (method B).

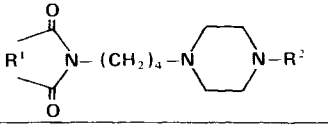
General Procedure for the Preparation of Compounds of Table IV. 5-[4-[4-(2-Pyrimidinyl)-1-piperazinyl]butyl]-tetrahydro-1*H*-thieno[3′,4′:3,4]cyclobuta[1,2-*c*]pyrrole-4,6-(3*H*,5*H*)-dione 2,2-Dioxide (63). Compound **63** was preprepared by method A with tetrahydro-1*H*-thieno[3′,4′:3,4]cyclobuta[1,2-*c*]pyrrole-4,6(3*H*,5*H*)-dione 2,2-dioxide (**11**), 1,4-dibromobutane, and 1-(2-pyrimidinyl)piperazine and was converted to the hydrobromide salt; mp 262–264 °C. Anal. ($C_{20}H_{27}SN_5O_4$·2HBr).

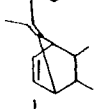
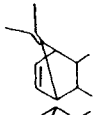
Compounds 64 and 65 were similarly prepared by use of the above procedure for the preparation of **63** with the exception that the appropriately substituted heteroarylpiperazine was used.

4,4a,5,5a,6,6a-Hexahydro-2-[4-(4-pyridinyl)butyl]-4,6-ethenocycloprop[*f*]isoindole-1,3(2*H*,3a*H*)-dione (66). To a

(20) Costall, B.; Naylor, R. J.; Nohvia, V. *Eur. J. Pharmacol.* **1978**, *50*, 39.

Table II. Polycyclic Aryl- and Heteroarylpiperazinyl Imides



Compound	R^1	R^2	mp. °C	% yield	formula[a]	inhibition of accumbens D_2 binding: K_i, nM (95%CI)[b], or % inhibn at 1 μM	inhibition of $5HT_{1A}$ binding[c]: k_i, nM (95%CI), or % inhibn at 1 μM	inhibition of CAR[d]: AB_{50}, mg/kg (95%CI)
13		2-pyrimidinyl	181–183	85	$C_{20}H_{29}N_5O_2 \cdot C_4H_4O_4$	374 (193–671)	N.T.[u]	6 (4–12),[v] > 40[w]
14		2-pyrimidinyl	192–194	59	$C_{21}H_{27}N_5O_2 \cdot C_4H_4O_4$[e]	248 (156–409)	42 (39–46)	5 (3–9),[v] > 40[w]
15		6-chloro-2-pyrazinyl	235–237	40	$C_{21}H_{26}ClN_5O_2 \cdot HCl$[f]	1%	74%	40[x]
16		6-chloro-3-pyridazinyl	258–261	41	$C_{21}H_{26}ClN_5O_2 \cdot HCl$	19%		40[y]
17		3-chloro-2-pyrazinyl	185–187	41	$C_{21}H_{26}N_5O_2Cl$[g]$\cdot HCl$[h]	48%	37 (31–44)	40[y]
18		2-pyrimidinyl	166–167	62	$C_{21}H_{29}N_5O_2 \cdot C_4H_4O_4$[e]$\cdot$		9 (6–13)	28 (26–30)[z]
19		2-pyrimidinyl	200–201	63	$C_{24}H_{31}N_5O_2 \cdot 2HCl$	50% at 10μM		> 40[w]
20		6-chloro-2-pyrazinyl	128–130	50	$C_{24}H_{30}N_5O_2Cl$[i]$\cdot 2HCl$[j]	968 (393–4170)		40[y]
21		2-pyrimidinyl	207–208	53	$C_{23}H_{29}N_5O_2 \cdot 2HCl$[f]	488 (194–1223)	38 (27–54)	40[y]
22		6-chloro-2-pyrazinyl	271–273	49	$C_{23}H_{28}ClN_5O_2 \cdot HCl$	690 (396–1409)	162 (123–212)	40 (34–49)[z]
23		6-chloro-3-pyridazinyl	271–272	48	$C_{23}H_{28}ClN_5O_2 \cdot HCl$	2334 (1100–8800)		40[y]
24		2-pyrazinyl	200–202	40	$C_{23}H_{29}N_5O_2 \cdot 2HCl$[f]	33%	68%	49 (31–212)[z]
25		5-trifluoro-methyl-2-pyridinyl	208–211	51	$C_{25}H_{29}F_3N_4O_2 \cdot 2HCl$[f]	40%	55%	40[y]
26		3-$CF_3C_6H_4$	218–220	62	$C_{20}H_{30}F_3N_3O_2 \cdot 2HCl$[e]	91%	26 (19–33)	44 (NCI)
27		2-$OCH_3C_6H_4$	210–213	72	$C_{26}H_{33}N_3O_3$[k]$\cdot 2HCl$	16 (11–24)	1.3 (0.8–2.0)	40[y]
28		3-ClC_6H_4	212–213	70	$C_{25}H_{30}ClN_3O_2 \cdot 2HCl$[e]	100%	14 (12–17)	40[y]

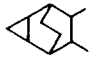
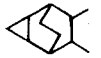
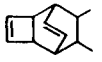
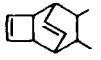
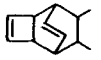
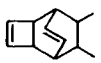
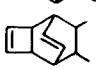
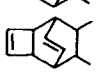
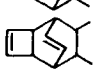
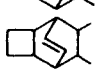
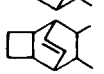
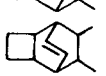
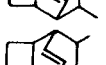
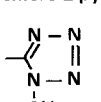
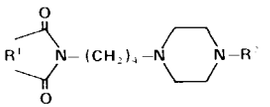
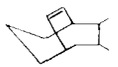
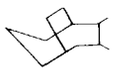
29		2-pyrimidinyl	190–192	68	$C_{23}H_{31}N_5O_2^l \cdot 2HCl^m$	140 (85–230)	14 (11–18)	34 (25–56)[z]
30		6-chloro-2-pyrazinyl	266–268	58	$C_{23}H_{30}ClN_5O_2 \cdot HCl$	49%	72%	40[x]
31		3-$CF_3C_6H_4$	242–244	95	$C_{26}H_{32}N_3F_3O_2 \cdot 2HCl$	92%	20 (14–27)	>40[w]
32		3-chloro-2-pyrazinyl	245–246	50	$C_{23}H_{30}ClN_5O_2 \cdot HCl$	75%	26 (20–34)	61 (NCI)[z]
33		6-chloro-2-pyrazinyl	>300[o]	46	$C_{24}H_{28}N_5ClO_2 \cdot 2HCl^i$	50%		40[y]
34		2-pyrimidinyl	252–254	68	$C_{24}H_{29}N_5O_2^n \cdot HCl$	59% 345 (233–520)	17 (13–21)	13 (NCI)
35		3-ClC_6H_4	225–227	41	$C_{26}H_{30}N_3ClO_2 \cdot 2HCl$	3%	41 (26–62)	>40[w]
36		2-$OCH_3C_6H_4$	233–235	50.3	$C_{27}H_{33}N_3O_3 \cdot 2HCl^e$	100%	100% 1.3 (1.0–1.5)	19 (14–27)[z]
37		5-trifluoro-methyl-2-pyridinyl	233–235	40	$C_{26}H_{29}N_4F_3O_2 \cdot 2HCl^f$	31%	40%	>40[w]
38		3-$CF_3C_6H_4$	227–228	82	$C_{27}H_{30}F_3N_3O_2 \cdot 2HCl$	96%	25 (18–35)	40 (NCI)[z]
39		2-pyrazinyl	>280	40	$C_{24}H_{29}N_5O_2 \cdot 2HCl^o$	13%	46%	40[y]
40		3-$CF_3C_6H_4$	222–223	81	$C_{27}H_{32}F_3N_3O_2 \cdot 2HCl$	99%	57 (34–90)	40[y]
41		3-ClC_6H_4	233–235	45	$C_{26}H_{32}ClN_3O_2 \cdot 2HCl$	87%	19 (11–31)	40[y]
42		2-pyrimidinyl	250–252	63	$C_{24}H_{31}N_5O_2 \cdot 2HCl^f$	85 (51–134)	1.3 (0.7–1.6)	47 (NCI)[z]
43		6-chloro-2-pyrazinyl	268–271	50	$C_{24}H_{30}ClNO_2^p \cdot HCl$	413	190 (152–238)	40[y]
44			266–268	59	$C_{22}H_{31}N_7O_2 \cdot HCl^e$	39%	47%	40[y]

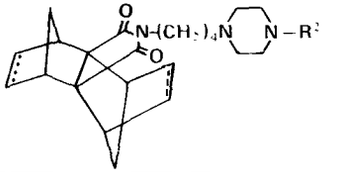
Table II (Continued)



Compound	R^1	R^2	mp, °C	% yield	formula[a]	inhibition of accumbens D_2 binding: K_i, nM (95%CI)[b], or % inhibn at 1 μM	inhibition of $5HT_{1A}$ binding[c]: k_i, nM (95%CI), or % inhibn at 1 μM	inhibition of CAR[d]: AB_{50}, mg/kg (95%CI)
45		2-pyrazinyl	208–210	51	$C_{24}H_{31}N_5O_2 \cdot 2HCl$[e]	48%	41 (35–49)	60 (NCI)[z]
46		6-chloro-3-pyridazinyl	283–285	44	$C_{23}H_{30}N_5ClO_2 \cdot 2HCl$[f]	1925 (1601–2377)		>40[w]
47		3-chloro-2-pyrazinyl	208–210	45	$C_{24}H_{30}ClN_5O_2^q \cdot HCl$[f]	74 (63–86)		40[y]
48		5-trifluoro-methyl-2-pyridinyl	254–256	51	$C_{26}H_{31}F_3N_4O_2^r \cdot 2HCl$[e]	65%	72%	>40[w]
49		6-chloro-2-pyrazinyl	273–275	53	$C_{24}H_{32}ClN_5O_2 \cdot HCl$[e]	65%	51 (42–61)	>40[w]
50		2-pyrimidinyl	237–240	59	$C_{24}H_{33}N_5O_2 \cdot 2HCl$[i]	53 (16–125)	1 (0.5–1.5)	40[y]
51		6-chloro-2-pyrazinyl	248–250	68	$C_{23}H_{32}ClN_5O_2 \cdot HCl$[f]	345 (202–643)	122 (101–146)	25 (21–30)[z]
52		2-pyrimidinyl	250–252	56	$C_{23}H_{31}N_5O_2^s \cdot 2HCl$	53%	12 (7–18)	40[y]
53		6-chloro-2-pyrazinyl	254–255	41	$C_{23}H_{30}ClN_5O_2^t \cdot HCl$[f]	43%	107 (91–125)	68 (NCI)[z]
54		2-pyrimidinyl	209–211	40	$C_{23}H_{31}N_5O_2 \cdot 2HCl$	74%	5 (4–7)	40[y]
55		6-chloro-2-pyrazinyl	274–276	47	$C_{23}H_{32}N_5ClO_2 \cdot HCl$	49%	162 (116–226)	>40[w]
56		5-trifluoro-methyl-2-pyridinyl	250–252	47	$C_{25}H_{33}N_4F_3O_2 \cdot 2HCl$[i]	33%	71%	>40[w]
57		3-$CF_3C_6H_4$	268–270	43	$C_{26}H_{34}N_4O_2F_3 \cdot 2HCl$	97%	17 (12–25)	>40[w]
	Buspirone					119 (NCI)	10 (6- 15)	5 (2.7–11.8)[v] 32 (NCI)[z]
	Ipsapirone (TVXQ–7821)						10 (6–14)	19 (14.6–31.5)[v] 42 (22–180)[z]

[a] All compounds had elemental analyses (C,H,N) within ± 0.4% of the theoretical values. [b] 95%CI indicates values for 95% confidence interval. [c] Rat hippocampal tissue. [d] Conditioned avoidance response. [e] Hemihydrate. [f] Hydrate. [g] C: calc, 50.6; found, 49.98; H: calc,6.40; found, 5.93. [h] Two and half hydrate. [i] N: calc, 12.6; found, 13.04. [j] Sesquihydrate. [k] C: calc, 61.41; found, 60.94. [l] H: calc, 7.2; found, 6.68. [m] Two and a quarter hydrate. [n] N: calc, 15.36; found, 14.95. [o] Dihydrate. [p] C: calc, 58.53; found, 58.03. [q] C: calc, 56.47; found, 55.94. [r] C: calc, 54.73; found, 54.29. [s] C: calc, 56.21; found, 56.69. [t] N: calc, 14.08; found, 14.88. [u] Not tested. [v] Active in shelf-jump CAR, ip. [w] Indicates insignificant activity in discrete trial CAR, p.o. [x] Active at single dose in discrete trial CAR, po. [y] Active at single dose in shelf-jump CAR, ip. [z] Active in discrete trial CAR, po.

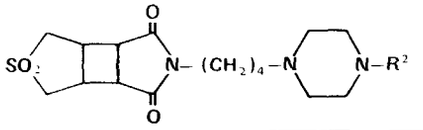
Table III. Polycyclic Heteroarylpiperazinyl Imides of Hexahydro 1,4:5,8-Dimethanonaphthalene-4a,8a-dicarboxylic Anhydride



Compound	–CH=CH–	R^2	mp. °C	% yield	formula[a]	inhibition of accumbens D_2 binding: K_i, nM (95%CI)[b], or % inhibn at 1 μM	inhibition of $5HT_{1A}$ binding[c]: k_i, nM (95%CI), or % inhibn at 1 μM	inhibition of CAR[k]: AB_{50}, mg/kg (95%CI)
58	–CH=CH–	6-chloro-2-pyrazinyl	262–265	49	$C_{26}H_{30}ClN_5O_2^e$•HCl	NT[d]	98%	>40[h]
59	–CH=CH–	2-pyrimidinyl	165–166	52	$C_{26}H_{31}N_5O_2$•2HCl[f]	53%	14 (10–19)	40[i]
60	–CH=CH–	2-pyrazinyl	272–275		$C_{26}H_{31}N_5O_2$•2HCl[g]	14%	129 (83–195)	40[i]
61	$–CH_2–CH_2–$	2-pyrimidinyl	223–225	50	$C_{26}H_{33}N_5O_2$•2HCl	63%	7 (6–8)	40[i]
62	$–CH_2–CH_2–$	6-chloro-2-pyrazinyl	244–246	53	$C_{26}H_{34}ClN_5O_2$•2HCl[f]	NT	23%	40[j]

[a] All compounds had elemental analyses (C,H,N) within ± 0.4% of the theoretical values. [b] 95%CI indicates values for 95% confidence interval. [c] Rat hippocampal tissue. [d] NT=Not tested [e] C: calc, 60.34; found, 59.77 [f] Hemihydrate. [g] Sesquihydrate. [h] Indicates insignificant activity in shelf jump CAR, ip. [i] Active at single dose in discrete trial CAR, p.o., [j] Active at single dose in shelf-jump CAR, ip. [k] Conditioned avoidance response.

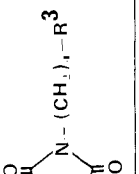
Table IV. Tetrahydrothienocyclobutapyrrole-4,6-dione 2,2-Dioxides



Compound	R^2	mp. °C	% yield	formula[a]	inhibition of accumbens D_2 binding: K_i, nM (95%CI)[b], or % inhibn at 1 μM	inhibition of $5HT_{1A}$ binding[c]: k_i, nM (95%CI), or % inhibn at 1 μM	inhibition of CAR[d]: AB_{50}, mg/kg (95%CI)
63	2-pyrimidinyl	262–264	54	$C_{20}H_{21}SN_5O_4^e$•2HBr[f]	0%	44%	>40[i]
64	6-chloro-2-pyrazinyl	154–156	49	$C_{20}H_{20}ClN_5SO_4^g$•HCl	0%	35%	40[j]
65	3-chloro-2-pyrazinyl	238–240	51	$C_{20}H_{20}ClN_5SO_4^h$•HCl	0%	28%	40[k]

[a] All compounds had elemental analyses (C,H,N) within ± 0.4% of the theoretical values. [b] 95%CI indicates values for 95% confidence interval. [c] Rat hippocampal tissue. [d] Conditioned avoidance response. [e] N: calc, 11.58; found, 11.03. [f] Hemihydrate. [g] Calc, C: 48.61 H: 5.35; N:13.88; found, C: 48.43; H: 4.84; N: 14.61. [h] N: calc, 13.88; found, 13.38. [i] Indicates insignificant activity in shelf-jump CAR,i.p. [j] Active at single dose in discrete trial CAR, po. [k] Active at single dose in shelf-jump CAR, ip.

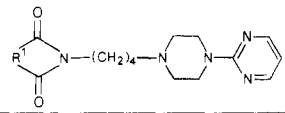
Table V. Polycyclic Alkylpyridines and Heteroalkylpiperidines



Compound	R'	R^3	mp, °C	% yield	formula[a]	inhibition of accumbens D_2 binding: K_i, nM (95%Cl)[b], or % inhibn at 1 μM	inhibition of $5HT_{1A}$ binding[c]: k_i, nM (95%Cl), or % inhibn at 1 μM	inhibition of CAR[d]: AB_{50}, mg/kg (95/Cl)
66		4-pyridinyl	228–230	48	$C_{20}H_{22}N_2O_2$·HCl	0%	0%	> 40[g]
67		4-pyridinyl	190–192	51	$C_{20}H_{24}N_2O_2$[e]·HCl[f]	6%	0%	40[h]
68			138–140	40	$C_{24}H_{29}ClN_4O_2$·HCl	21%	8%	40[h]

[a] All compounds had elemental analyses (C,H,N) within ± 0.4% of the theoretical values. [b] 95%Cl indicates values for 95% confidence interval. [c] Rat hippocampal tissue. [d] Conditioned avoidance response. [e] C: calc, 64.95; found, 65.42. [f] Hemihydrate. [g] Indicates insignificant activity in shelf-jump CAR, ip. [h] Active at single dose in shelf-jump CAR, ip.

Table VI. Effect of Lipophilicity of the Polycyclic Imides on the Affinity for the 5-HT_{1A} Receptor Binding Sites



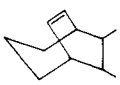
Compound	R	Log P	Inhibition of 5-HT_{1A} Binding, k_i, nM(95%Cl)
14		1.36	42(39-46)
21		1.73	38(27-54)
34		1.79	17(13-21)
29		1.83	14(11-18)
52		1.94	12(7-18)
42		2.02	1.3(0.7-1.6)
50		2.09	1 (0.5-1.5)

Table VII. Effects of the Polycyclic Aryl- and Heteroarylpiperazinyl Imides and Buspirone on Apomorphine Antagonism[a]

Compound	ED_{50} mg/kg, i.p. (95% Cl)[b] Stereotyped Behavior	Climbing Behavior	Ratio ED_{50}, Stereotyped Behavior/ ED_{50} Climbing Behavior
24	33(29-37)	14(9-23)	2.35
26	Inactive	22(13-35)	---
27	10(6-16)	10(NO Cl)	1
34	23(18-29)	3(1.6-7.6)	7.60
45	32(NO Cl)	15(11-20)	2.10
Buspirone	Inactive[c]	Inactive	---

[a] Low-dose APO-induced behavior [b] 95% Confidence intervals [c] ED_{50} > 60 mg/kg, i.p.

stirred solution of 1,3-dioxo-2*H*-4,6-etheno-1,3,3a,6a-tetrahydrocycloprop[*f*]isoindole (4) (2.2 g, 0.11 mol) in 50 mL of dimethylformamide were added cesium carbonate (3.0 g, 0.011 mol) and 4-pyridinylbutyl bromide hydrobromide (3.2 g, 0.011 mol). The reaction mixture was stirred at room temperature for 48 h; dimethylformamide was evaporated under reduced pressure and the residue was extracted with methylene chloride (3 × 200 mL). The methylene chloride extracts were collected, washed with water, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The semisolid residue was subjected to preparative HPLC and separated with ethyl acetate as the eluent. Evaporation of the solvent from the desired fractions afforded 1.6 g (45% yield) of the title compound, which was converted to the hydrochloride salt by dissolving the free base in ethanol and adding ethanol saturated with hydrogen chloride; mp 228–230 °C. Anal. ($C_{20}H_{22}N_2O_2$·HCl).

2-[4-[1-(6-Chloro-2-pyrazinyl)-4-piperidinyl]butyl]-4,4a,5,5a,6,6a-hexahydro-4,6-ethenocycloprop[*f*]isoindole-1,3(2*H*,3a*H*)-dione (68). To an ethanolic solution of the compound of **66** (2 g, 0.006 mol) in 50 mL of ethanol under nitrogen were added 0.4 g of rhodium over aluminum oxide and 1 mL of glacial acetic acid. The reaction mixture was hydrogenated at room temperature in a Parr shaker with hydrogen (50 psi) for 3 h. It was then filtered and the solvent was removed under reduced pressure. The remaining oil was dissolved in 50 mL of dimethylformamide and to that solution was added 0.5 g of cesium carbonate and 2,6-dichloropyrazine (1.4 g, 0.007 mol). The reaction mixture was stirred at room temperature for 48 h, and via the same workup used for compound **66**, it afforded the title compound, which was converted to the hydrochloride salt; mp 138–140 °C. Anal. ($C_{24}H_{29}ClN_4O_2$·HCl).

Antagonism of Apomorphine-Induced Behaviors. (For the high-dose procedure, see ref 17). Antagonism of low-dose APO-induced stereotyped and climbing behavior tests were conducted according to an adaptation of the methods of Costall et al.[20] and

Puech et al.[21] Male mice (20–25 g, CF-1, Charles River) were housed seven/cage with food and water ad libitum. Animals were allowed to acclimate for at least 3 days after arrival before they were tested. Test compounds, suspended or solubilized in 0.25% Tween 80, were administered ip at several dose levels (1, 10, 30, and 60 mg/kg) to male mice (six mice/dose level). A control group, run simultaneously with drug groups, received 0.25% Tween 80 at equal volumes. Thirty minutes later, experimental and control animals were challenged with 1 mg/kg sc apomorphine. Five minutes after the apomorphine injection, the sniffing–licking–gnawing (0 = absent, 1 = present) syndrome (stereotyped behavior) and climbing behavior (0 = all four feet on ground, 1 = two feet up on wire cage, 2 = all four feet up on wire cage) induced by apomorphine were scored and recorded for each animal. Readings were repeated every 5 min during a 30-min test session. Scores were totaled over the 30 min test session for each syndrome (stereotyped behavior and climbing). ED_{50} values (95% confidence intervals) were calculated for inhibition of apomorphine-induced stereotyped and climbing behavior with a nonlinear least-squares calculation with inverse prediction. Higher potencies in antagonizing climbing than stereotyped behavior may indicate potential antipsychotic activity with low extrapyramidal side effect liability.[17]

Shelf-Jump Conditioned Avoidance. Conditioned avoidance tests were conducted according to an adaption of the method of Herman et al.[22] Male CD rats (Charles River) maintained at approximately 400–450 g body weight were used. Previously trained rats were placed in plexiglass experimental chambers divided into two sections: a main chamber ($10^1/_2$ in. × $6^3/_4$ in. × $11^7/_8$ in. high) and an elevated chamber or shelf ($5^7/_8$ in. × $6^7/_8$ in. × $5^3/_4$ in.). A moveable wall, controlled by a motor, determined whether the rat had access to the shelf at any time during the experiment. The experimental chamber also contained a house light and sonalert. A steel grid floor in the main chamber was wired for presentation of electric shock. Each trial consisted of a 15-s warning tone (conditioned stimulus), continuing for an additional 15 s accompanied by electric shock (unconditioned stimulus). A response (jumping onto the exposed shelf of the upper chamber) occurring during the initial 15-s warning tone was considered an avoidance response, while a response occurring during shock delivery was considered an escape response. Trials were presented on a fixed interval schedule of 1 min. The session consisted of 36 trials. Animals were run twice weekly with control sessions always preceding a drug run and with at least one day intervening. Compounds were administered ip or po at appropriate pretreatment times to a minimum of five rats at each dose level over a range of doses. The following experimental parameters were recorded by computer: (1) the number of avoidance responses, (2) the number of escape responses, and (3) the number of trials in which no response occurred. These data were used to calculate the percent difference from control values previously determined and were presented for visual comparison via a line graph. Response counts were summed over all subjects at a given dose. The number of trials in which rats failed to exhibit an avoidance response (avoidance Block, AB) was determined at each dose. This number was expressed as a percentage of the total trials. Control performance was arbitrarily assigned a value of 100% for avoidance and the dose calculated to produce a 50% block in avoidance responding (AB_{50}) was obtained from a dose–effect regression line fitted by the method of least squares.

Discrete Trial Conditioned Avoidance. Conditioned avoidance tests were conducted in male CD rats (Charles River) maintained at approximately 400–450 g body weight. Rats trained previously were placed in plexiglass experimental chambers equipped with a response lever, house light, and sonalert. A steel grid floor was wired for presentation of electric shock. Each trial consisted of a 15-s warning tone (conditioned stimulus), continuing for an additional 15 s accompanied by electric shock (unconditioned stimulus). The rat could terminate a trial at any point by depressing the response lever. A response during the initial 15-s warning tone ended the trial before shock delivery and was considered an avoidance response, while a response occurring during shock delivery was an escape response. Trials were presented on a variable interval schedule of 2 min. The session consisted of 60 trials. Animals were run two to three times weekly with control sessions always preceding a drug run and with at least one day intervening. Compounds were administered ip or po at a pretreatment time of 30 min to a minimum of five rats at each dose level (20 or 40 mg/kg) or over a range of doses. The following experimental parameters were recorded by computer: (1) the number of intertrial interval responses, (2) the number of avoidance responses, (3) the number of escape responses, and (4) the number of trials in which no response occurred. These data were used to calculate the percent difference from control values previously determined. For active compounds, response counts were summed over all subjects at a given dose. The number of trials in which rats failed to exhibit an avoidance response (avoidance block, AB) was determined at each dose. This number was expressed as a percentage of the total trials. Control performance was arbitrarily set at 100% for avoidance responding and the dose calculated to produce a 50% block in avoidance responding (AB_{50}) was obtained from a dose–effect regression line fitted by the method of least squares.

D_2 Receptor Binding Assay. Dopamine-2 (D_2) receptor affinity was measured in limbic brain tissue by using a modification of the method of Fields et al.[23] and Bennett.[24] Several rats (Sprague–Dawley; 180–260 g) were decapitated and the brains were rapidly removed. Limbic brain tissue (nucleus accumbens, septal area, olfactory tubercle) was dissected and homogenized on ice in 9 volumes of buffer (50 mM Tris·HCl, 120 mN NaCl, 5 mM KCl, 1 mM $CaCl_2$, 0.1% L-ascorbic acid, 10 μM pargyline hydrochloride, pH 7.1) with a Polytron homogenizer at setting 5 for three 15-s bursts. The homogenate was then diluted 4-fold with buffer and centrifuged at 30000*g* for 20 min, and the supernatant was discarded. The pellet was resuspended in the same volume of buffer and recentrifuged as before, again discarding the supernatant. This pellet was then resuspended in the same volume of buffer used in the homogenization, and the protein content of this preparation was assayed by the method of Lowry et al.[25] The homogenate was stored frozen at −70 °C until use.

Thirty microliters of the homogenate (0.2–0.3 mg of protein/sample) were incubated with 0.3 nM [^{3}H]spiroperidol (New England Nuclear) and various concentrations of test drug in a final volume of 1 mL in the above buffer for 10 min at 37 °C water bath. At the end of the incubation, 3 mL of cold 50 mM Tris·HCl, pH 7.7, were added to each tube, and the contents were rapidly vacuum-filtered through Whatman GF/B glass-fiber filters. The filters were then rapidly washed three times with 3 mL of the same buffer, placed in scintillation vials, and shaken for 15 min with 10 mL of Hydrofluor (National Diagnostics) scintillation cocktail. The vials were then counted in a Packard 460CD scintillation counter.

Specific binding was defined as total binding less binding in the presence of 1 μM (+)-butaclamol. Binding in the presence of various concentrations of test drug was expressed as a percent of specific binding when no drug was present. These results were then plotted as logit percent binding vs log concentration of test drug. Linear regression analysis then yields a straight line with 95% confidence limits from which an IC_{50} can be inversely predicted. K_i (inhibition constant) for the test drug was then calculated by the formula:[26]

$$K_i = \frac{IC_{50}}{1 + [[^3H]\text{Spiroperidol}]/K_D}$$

where K_D = 0.3 nM for spiroperidol binding.

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5-HT_{1A} Receptor Binding Assay. 5-HT_{1A} receptor affinity was measured in hippocampal rat brain tissue by using a modification of the method of Hall et al.[27] Several rats were decapitated and the brains were rapidly removed. Hippocampal tissue was dissected and homogenized on ice in 40 volumes of buffer A (50 mM Tris·HCl, pH 7.7) with a Polytron homogenizer at setting 5 for three 15-s bursts. The homogenate was then centrifuged at 48000*g* for 10 min and the supernatant discarded. The pellet was resuspended in 40 volumes of the same buffer and incubated at 37 °C for 10 min to aid in the removal of endogenous serotonin. The homogenate was then centrifuged (as above) and the supernatant discarded. The pellet was then resuspended in 100 volumes of buffer B (50 mM Tris·HCl, pH 7.7 containing 0.1% ascorbate, 10 μM pargyline, and 4 mM $CaCl_2$) and sonicated. An aliquot was taken for protein determination by the Lowry method[25] and the remainder stored frozen at −70 °C until used.

The homogenate (500 μL; 0.4–0.6 mg of protein/sample) was incubated with 100 μL (1.5–1.8 nM) [^{3}H]-8-hydroxy-2-(di-*n*-propylamino)tetralin and various concentrations of test drug in a final volume of 2 mL of buffer B for 10 min at 37 °C. At the end of the incubation, 3 mL of cold buffer A was added to each tube, and the contents were rapidly filtered through Whatman GF/B glass filters. The filters were then rapidly washed two times with 3 mL of the same buffer, placed in scintillation vials, and shaken for 15 min with 10 mL of Hydrofluor (National Diagnostics) scintillation cocktail. The vials were then counted in a Packard 460 CD scintillation counter.

Specific binding was defined at total binding less binding in the presence of 1 μM (+)-serotonin. Results of 5-HT_{1A} receptor binding studies were analyzed as previously stated for the D_2 receptor binding studies. The K_D value for [^{3}H]-8-OH-DPAT binding in hippocampus was 1.8 nM.

Acknowledgment. Thanks to B. Hofmann and his staff for NMR determination, Alice Conti for octanol–water partition coefficient determinations, Charles Kuhlman and his staff for HPLC and microanalytical work, Charles Lin for providing intermediate **11**, and Mary Ellen Fiala and Janet McKay for typing the manuscript.

Registry No. 4, 25547-30-2; **5**, 114298-16-7; **6**, 6295-73-4; **7**, 6705-94-8; **8**, 114222-40-1; **9**, 23852-39-3; **10**, 17397-36-3; **11**, 33974-23-1; **12** (R^2 = 2-pyrimidinyl), 33386-20-8; **12** (R^2 = 2-pyrazinyl), 114222-98-9; **12** (R^2 = 6-chloro-2-pyrazinyl), 114222-99-0; **13**, 102995-93-7; **13**·$C_4H_4O_4$, 102995-94-8; **14**, 103066-37-1; **14**·$C_4H_4O_4$, 103066-38-2; **15**, 110944-39-3; **15**·HCl, 110944-62-2; **16**, 114222-41-2; **16**·HCl, 112050-66-5; **17**, 110944-42-8; **17**·HCl, 112025-11-3; **18**, 103066-39-3; **18**·$C_4H_4O_4$, 103066-40-6; **19**, 114222-42-3; **19**·2HCl, 114222-72-9; **20**, 114222-43-4; **20**·2HCl, 114222-73-0; **21**, 110944-33-7; **21**·2HCl, 110944-54-2; **22**, 110944-28-0; **22**·HCl, 110944-63-3; **23**, 110944-35-9; **23**·HCl, 114222-74-1; **24**, 110944-48-4; **24**·2HCl, 110944-68-8; **25**, 114222-44-5; **25**·2HCl, 114222-75-2; **26**, 114222-45-6; **26**·2HCl, 114222-76-3; **27**, 114222-46-7; **27**·2HCl, 114222-77-4; **28**, 114222-47-8; **28**·2HCl, 114222-78-5; **29**, 110944-29-1; **29**·2HCl, 114222-79-6; **30**, 110944-49-5; **30**·HCl, 110944-69-9; **31**, 114222-48-9; **31**·2HCl, 114222-80-9; **32**, 110944-50-8; **32**·HCl, 112025-10-2; **33**, 114298-17-8; **33**·2HCl, 114374-96-8; **34**, 114298-18-9; **34**·HCl, 114374-97-9; **35**, 114222-49-0; **35**·2HCl, 114298-21-4; **36**, 114222-50-3; **36**·2HCl, 114298-22-5; **37**, 114298-19-0; **37**·2HCl, 114374-98-0; **38**, 114222-51-4; **38**·2HCl, 114298-23-6; **39**, 114298-20-3; **39**·2HCl, 114374-99-1; **40**, 114222-52-5; **40**·2HCl, 114222-81-0; **41**, 114222-53-6; **41**·2HCl, 114222-82-1; **42**, 110944-41-7; **42**·2HCl, 110944-61-1; **43**, 110944-40-6; **43**·HCl, 114222-83-2; **44**, 114222-54-7; **44**·HCl, 114222-84-3; **45**, 110944-51-9; **45**·2HCl, 110944-70-2; **46**, 114222-55-8; **46**·2HCl, 114222-85-4; **47**, 110944-36-0; **47**·HCl, 114222-86-5; **48**, 114222-56-9; **48**·2HCl, 114222-87-6; **49**, 110944-31-5; **49**·HCl, 110944-57-5; **50**, 110944-32-6; **50**·2HCl, 110944-58-6; **51**, 110944-34-8; **51**·HCl, 114222-88-7; **52**, 110944-45-1; **52**·2HCl, 110944-65-5; **53**, 110944-46-2; **53**·HCl, 110944-66-6; **54**, 114222-57-0; **54**·2HCl, 110944-72-4; **55**, 114222-58-1; **55**·HCl, 114222-89-8; **56**, 114222-59-2; **56**·2HCl, 114222-90-1; **57**, 114222-60-5; **57**·2HCl, 114222-91-2; **58**, 114222-61-6; **58**·HCl, 114298-24-7; **59**, 114222-62-7; **59**·2HCl, 114298-25-8; **60**, 114222-63-8; **60**·2HCl, 114298-26-9; **61**, 114222-64-9; **61**·2HCl, 114298-27-0; **62**, 114222-65-0; **62**·2HCl, 114298-28-1; **63**, 114222-66-1; **63**·2HBr, 114222-92-3; **64**, 114222-67-2; **64**·HCl, 114222-93-4; **65**, 114222-68-3; **65**·HCl, 114222-94-5; **66**, 114222-69-4; **66**·HCl, 114222-95-6; **67**, 114222-70-7; **67**·HCl, 114222-96-7; **68**, 114222-71-8; **68**·HCl, 114222-97-8; maleimide, 541-59-3; maleic anhydride, 108-31-6; 1,3,5,7-cyclooctatetraene, 629-20-9; 1,3-cycloheptadiene, 4054-38-0; 1,3-cyclooctadiene, 1700-10-3; norbornadiene-2,3-dicarboxylic anhydride, 17397-31-8; cyclopentadiene, 542-92-7; sulfolene, 77-79-2; 2-(4-bromobutyl)hexahydro-4,7-etheno-1*H*-cyclobut[*f*]isoindole-1,3(2*H*)-dione, 114222-39-8; 1-(2-pyrimidinyl)piperazine, 20980-22-7; 4-pyridinylbutyl bromide, 109315-44-8; 2,6-dichloropyrazine, 4774-14-5; 1-(6-chloro-2-pyrazinyl)piperazine, 64022-27-1; 1-(3-chloro-2-pyrazinyl)piperazine, 85386-99-8.

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Synthesis and Dopamine Agonist and Antagonist Effects of (*R*)-(−)- and (*S*)-(+)-11-Hydroxy-*N*-*n*-propylnoraporphine

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The *R*-(−) and *S*-(+) enantiomers of 11-hydroxy-*N*-*n*-propylnoraporphine, (*R*)-**3** and (*S*)-**3**, were synthesized in six steps from 1-(3-methoxy-2-nitrobenzyl)isoquinoline. Neuropharmacological evaluation of the *R* and *S* isomers (by affinity to dopamine receptor sites in rat brain tissue, induction of stereotyped behavior, and interaction with motor arousal induced by (*R*)-apomorphine in the rat) indicated that, similar to the 10,11-dihydroxy congener **2**, both enantiomers can bind to dopamine receptors but that only (*R*)-**3** activates them, whereas (*S*)-**3** shows activity as a dopaminergic antagonist.

Absolute configuration is critically important for interactions at dopamine (DA) receptors.[1,2] Only the *R*-(−) enantiomer of apomorphine, obtained by the acid-catalyzed rearrangement of the natural product (−)-morphine, possesses DA agonist activity.[3] In contrast, (*S*)-(+)-bulbocapnine, a naturally occurring aporphine alkaloid, has DA receptor antagonist activity and its absolute configuration at carbon 6a is opposite to that of (*R*)-(−)-apomorphine.[4] It has been suggested that (*S*)-(+)-apo-

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