Table III. Biological Activities[a]

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

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

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

Experimental Section

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

1,4-Bis(3-indoleglyoxyloyl)piperazine (1). Piperazine (2.6 g, 30 mmol) in dry 1,2-DME (100 ml) was stirred while 3-indoleglyoxyloyl chloride (4.3 g, 20 mmol) in 1,2-DME (25 ml) was added dropwise. The resulting precipitate was collected, suspended in H_2O, and stirred for 30 min, then collected again, washed with H_2O, and dried to give the product as a colorless solid (4.3 g).

Other 1,4-bis(3-indoleglyoxyloyl)piperazines in Table I were prepared in a similar manner, with recrystallisation from DMF–H_2O when necessary.

1,4-Bis(indol-3-ylethyl)piperazine (14). Method A. Compound **1** (1.0 g, 2.25 mmol) was suspended in dry 1,2-DME (100 ml) and $LiAlH_4$ (1.0 g, 26 mmol) was added. The mixture was stirred under reflux for 24 hr. Excess $LiAlH_4$ was decomposed by dropwise addition of H_2O, the inorganic material was filtered off, and the filtrate was evaporated to give a colorless oil which crystallized on scratching. Recrystallization from EtOH–H_2O gave the product as colorless needles (0.6 g).

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

Method B. A mixture of 3-(2-bromoethyl)indole (44.8 g, 0.2 mol), piperazine (8.6 g, 0.1 mol), and diisopropylamine (30.3 g, 0.3 mol) in DMF (200 ml) was stirred at room temperature for 18 hr. The precipitated diisopropylamine hydrobromide was filtered off and the filtrate was poured onto ice–water. A gum formed which solidified on scratching. The solid was collected, washed, dried, and recrystallized from EtOH–H_2O to give colorless needles of 1,4-bis(indol-3-ylethyl)piperazine (28.0 g).

1,4-Bis[2-(1-methyl-3-indolyl)ethyl]piperazine (26). Method C. Compound **14** (7.46 g, 20 mmol) was added to a stirred solution of sodium amide in liquid ammonia (500 ml). Methyl iodide (5.8 g, 41 mmol) in Et_2O (100 ml) was added dropwise to the stirred mixture; then the ammonia was allowed to evaporate overnight. Et_2O (200 ml) was added to the residue, followed by H_2O (200 ml) added dropwise at first. The insoluble material (7.0 g) was collected, dried, and recrystallized from EtOH to give the product (5.7 g) as colorless needles. Compounds **27–30** were prepared in a similar manner.

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

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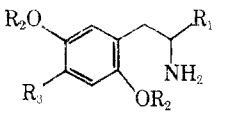
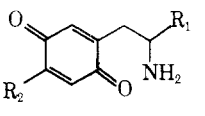
Recent studies in a number of laboratories have described the unique pharmacologic properties of 2-(2,4,5-trihydroxyphenyl)ethylamine (**1**) commonly referred to as 6-hydroxydopamine.[1] When administered intravenously,

amine 1 leads to the irreversible depletion of norepinephrine and selective destruction of noradrenergic terminals in peripheral organs.[2] This compound has been described as both an enzymatically[3] and spontaneously[4] formed oxidation product of dopamine. When exposed to air in solution at basic pH compound 1 is rapidly oxidized to the *p*-quinone species 2 which then undergoes intramolecular cyclization. Earlier reports in the literature suggested[5] that this cyclization involves a 1,4 Michael-type reaction to yield a trihydroxyindoline. However, recent evidence[6] has confirmed a previously described[7] pathway proceeding by 1,2 Schiff base formation and leading eventually to 5,6-dihydroxyindole (3). The possibility that the *p*-quinone 2 may also undergo intermolecular covalent bond formation with nucleophilic moieties of macromolecules has been offered as an explanation for the ability of this molecule to destroy noradrenergic terminals.[8] Consistent with this proposal, tritium-labeled 1 has been shown to form irreversible bonds with proteins.[9] The polarity of 6-hydroxydopamine precludes its passage across the blood brain barrier, although irreversible depletion of brain norepinephrine stores has been reported for centrally administered 6-hydroxydopamine.[10]

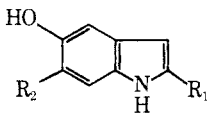
Our interest[11] in the metabolism and mechanism of action of the psychotomimetic compound 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (4), commonly referred to as "DOM," and the structural analogy between 6-hydroxydopamine and the bis-O-demethylated compound 5, a potential metabolite of amine 4 (for examples of oxidative O-demethylations, see ref 12), has prompted us to prepare the *p*-hydroquinone 5 as an aid to its identification in the urine of animals treated with 4 and in tissue homogenates of 4.



1, $R_1 = R_2 = H$; $R_3 = OH$
4, $R_1 = R_2 = R_3 = CH_3$
5, $R_1 = R_3 = CH_3$; $R_2 = H$

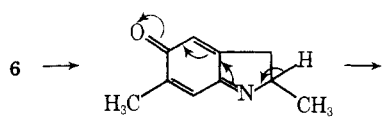


2, $R_1 = H$; $R_2 = OH$
6, $R_1 = R_2 = CH_3$

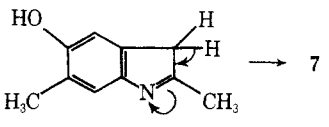


3, $R_1 = H$; $R_2 = OH$
7, $R_1 = R_2 = CH_3$

Aqueous hydrobromic acid treatment of amine 4 followed by attempted isolation of the aminophenol 5 at pH 9.5 provided a compound in good yield which proved to be not the desired product 5 but rather 5-hydroxy-2,6-dimethylindole (7). Chemical ionization mass spectral (cims)[13] analysis gave a molecular ion (MH^+) at 162 corresponding to protonated 7. The nmr spectrum showed three one-proton singlets for the aromatic protons and two three-proton singlets for the methyl protons. A literature search established that compound 7 has been previously synthesized by the Nenitzescu reaction[14] *via* hydrolysis and decarboxylation of the condensation product obtained from ethyl 3-aminocrotonate and *p*-toluquinone.



8



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Formation of compound 7 under the conditions reported here may be rationalized by assuming that the *p*-hydroquinone 5 suffers air oxidation at pH 9.5 to yield the quinone 6 which then undergoes cyclization to the quinoneimine 8. Subsequent proton shifts (8 → 9 → 7) lead to the final product 7.

In order to substantiate this mechanism in our system, the HBr hydrolysate of amine 4 was worked up by cation exchange chromatography which provided the desired *p*-hydroquinone 5 as its HCl salt. The uv spectrum of this product showed a characteristic $\pi \rightarrow \pi^*$ absorption at 296 nm. When a drop of dilute base was added, the solution turned immediately yellow and then over a period of several seconds became colorless again. The resulting stable uv spectrum was identical with the spectrum of the indole 7 in dilute base. Presumably the transient yellow color is due to the *p*-quinone 6. The fact that the spectrum of compound 7 is obtained in less than 1 min suggests that indole formation at pH 9.5 is a facile process.

Preliminary results on the pH and oxygen dependency of the oxidation of the hydroquinone have shown that aqueous solutions of 5 at pH 5 are stable (no change in ultraviolet absorption spectrum on standing for several hours). However, at pH 7.4 in an oxygen-dependent transformation, the initial spectrum, λ_{max} 284 nm (ϵ 2800), changes over a 20-min period to λ_{max} 281 nm (ϵ 29,000), indicating the formation of a new chromophore. Upon standing overnight or within a few seconds upon treatment with base, this intermediate is converted to indole 7 (identified by its uv and mass spectra). These data suggest that the intermediate may be an equilibrium mixture of quinone 6 and quinoneimine 8.

The generality of this reaction sequence and its potential importance in the metabolism and mechanism of action of amine 4 are currently under investigation. Should the *p*-hydroquinone 5 or indole 7 be detected as a metabolite of 4, it will be of great interest to examine the effects of compound 5 on central noradrenergic activity. It has been suggested that the aberrant formation of 6-hydroxydopamine (1) in the brain may account for spontaneous mental dysfunction.[15] An analogous argument to account for the chemically affected alterations in CNS function by amine 1 provides an interesting description of molecular events which may be associated with psychotomimesis.

Experimental Section

All reactions were performed under a nitrogen or argon atmosphere, and solvents were removed on a rotary evaporator under vacuum. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Nmr spectra were recorded on a Varian A-60A instrument. Chemical shift values are reported in parts per million relative to TMS ($CDCl_3$) or DSS (D_2O). Ir spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer. The chemical ionization mass spectra were recorded on an AEI MS-902 spectrometer using isobutane (0.7 Torr) as reagent gas. The uv spectra were recorded on a Cary 15 spectrophotometer. Microanalyses were performed by the Microanalytical Laboratory, University of California, Berkeley.

1-(2,5-Dihydroxy-4-methylphenyl)-2-aminopropane Hydrochloride (5·HCl). A solution of 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane[16] (4, 5.00 g, 0.0239 mol) in freshly distilled 48% HBr (35 ml) was heated under reflux with stirring for 6 hr under dry Ar. The cooled reaction mixture was concentrated under vacuum, taken up in 3 ml of H_2O, and made to pH 2–3 by dropwise addition of 15% NaOH. The reaction mixture was chromatographed on a Dowex 50W-X4 cation exchange column (prepared by washing 25.0-g packing with 200 ml of 2 *N* HCl and then 200 ml of distilled H_2O). The column was washed with distilled

H_2O until the washings showed a negative $AgNO_3$ test for halide (150 ml). The amine was then eluted with 200 ml of 4 *N* HCl. The presence of the product in each fraction was determined by observing a yellow color after the addition of a few drops of 15% NaOH to a small aliquot. The eluent was concentrated under vacuum to give a white solid which was filtered in hot MeOH. The addition of a few drops of Et_2O led to crystallization of amine hydrochloride (2.45 g, 0.0112 mol, 47%). The analytical sample was obtained by recrystallization from 2-propanol-Et_2O: mp 226–227.5° dec; nmr (D_2O) δ 6.85 (s, Ar), 6.81 (s, Ar), 3.75 (m, CH), 2.95 (d, CH_2), 2.24 (s, $ArCH_3$), 1.42 ppm (d, CH_3); ir (KBr) 3460 (OH stretch), 3240 (OH stretch), 2970 cm^{-1} (NH_3^+); uv (absolute EtOH, 2.1 mg/100 ml) λ_{max} 296 nm (ε 4000), 318 (sh, 5000); uv (1 min after addition of 1 drop of 1% NaOH) λ_{max} 296, 273 nm. The absorbances indicated essentially complete conversion of **5** to **7**. A transient absorbance at 435 nm with a half-life of a few seconds was observed immediately upon addition of a drop of 1% NaOH to a solution of **5**·HCl. *Anal.* ($C_{10}H_{15}NO_2$) C, H, N.

5-Hydroxy-2,6-dimethylindole (7). A solution of 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (**4**, 1.60 g, 0.00766 mol) in 10 ml of 48% HBr was held at reflux for 12 hr and then poured into 50 ml of ice H_2O. The pH of the aqueous mixture was adjusted to 9.5 by careful addition of concentrated NH_4OH. After stirring overnight in air, the crude indole was extracted with 2 × 60 ml of Et_2O; the Et_2O was dried ($MgSO_4$) and concentrated to give 1.5 g of solid. Sublimation (115–118°, 100 μ) provided 0.835 g (0.00518 mol, 68%) of a colorless solid. Recrystallization from PhH–Et_2O gave the pure product: mp 180–183° (lit.[14] mp 183–184°); nmr ($CDCl_3$) δ 7.00, 6.85, 5.92 (s, Ar), 2.35, 2.26 ppm (s, CH_3); uv (absolute EtOH, 2.30 mg/100 ml) λ_{max} 296 nm (ε 5700), 274 (7000); uv (30 sec after addition of 1 drop of 1% NaOH) λ_{max} 296 nm (ε 5200), 273 (6900).

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Quantum Statistical Calculation for the Correlation of Biological Activity and Chemical Structure. 2. Drug-Membrane Penetrations

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In part 1[1] it was shown that drug actions could be correlated in terms of drug-receptor interactions through the use of the quantum statistical concept. Infrared spectroscopic data for given functional groups were used as the independent variable in a linear regression. The theoretical background is based on the probability of binding a set of receptor sites with active centers of a drug molecule. This probability is related to the partition function of statistical mechanics, and the partition function is associated with quantum energy levels of drug molecules, which are observable by various spectral techniques. The main feature of this correlation is to avoid the tedious procedure of quantum chemical calculations, though the calculations are fascinating and interesting.

In part 1 we also discussed the variable *p*(Brownian) which is associated with the probability of a drug molecule's passing through biological membranes. At that time we mentioned the possibility of publishing the theoretical derivation of *p*(Brownian) in part 2. We now proceed to do this by identifying this variable with the lipophilic parameter[2-6] π, which is defined as log (P_x/P_h) where P_h and P_x are, respectively, the partition coefficients of the parent compound and its derivatives between the organic phase and the aqueous phase. Two variables are used for the correlation of biological activity and chemical structure. First, spectroscopic data (including uv and ir) are used to express the probability of adsorption between the receptors and the drug molecules. Second, the parameter π, the relative lipophilicity, is used as a measure of the penetration ability of the drug molecules.

Theoretical Method. The same postulate as in part 1 is made; *i.e.*, the rate of biological response is expressed in the simple form

$$\frac{d(\text{biological response})}{dt} = AC \times p^{a1}(\text{Brownian}) \times p^{a2}(\text{binding}) \quad (1)$$

where *C* is the drug concentration, *p*(Brownian) is the probability of successful penetration of a drug molecule in the Brownian-like motion (see Figure 1) through biomembranes to reach a receptor, *p*(binding) is the probability of a successful binding between a drug molecule and a receptor, and a1 and a2 are constants.

To derive *p*(Brownian) we shall assume a simple physical model which can be handled mathematically. In Figure 1 a drug molecule is moving from the origin to the receptor site, with **r** representing the position vector in two-dimensional version. A drug molecule has made *M* steps (the length of each step is *a*) from the origin in the extracellular phase to reach the receptor site which is located *l* units from the origin. Each step of the movement can be in the states $i = 1, 2, 3, \ldots, n$ with partition function $j_i(T)$† and length l_i. Suppose a net attraction force of the lipophilicity τ is applied in the biomembrane to pull in the drug molecule in the extracellular fluid. The partition function for this system is

$$\Delta(\tau, M, T) = \xi(\tau, T)^M \quad (2)$$

†For a similar model used in polymer chemistry see ref 7.