3. Compounds 1, 2, and 4 demonstrate antiinflammatory activity at 40 mg/kg while 3 does not differ from the control group. Such data point out that 2 shows a greater antiinflammatory activity compared to the other compounds at all doses tested.

Seventh Hour Results. Compounds 1, 2, and 3 show antiinflammatory activity at 5 and 20 mg/kg. At 40 mg/kg only 1 and 2 maintain their effect, while 3 causes an increased foot volume. Compound 4 is inactive at 5 mg/kg. The pharmacological data indicate that, in this series, compound 2 is the most active.

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Lysergic Acid Diethylamide. Photoelectron Ionization Potentials as Indices of Behavioral Activity

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The photoelectron spectrum of lysergic acid diethylamide (LSD) reveals five ionization potentials (IP's) between 7.25 and 9.75 eV arising from the aromatic (π) portion of the molecule and IP's of 8.4 eV arising from the tertiary amine and 8.5–9.0 and 9.1 eV arising from the amide group. Comparisons of the IP's of LSD, and of phenethylamines and tryptamines reported by us elsewhere, with activities of these compounds in rat and human behavioral tests show that increasing activity is paralleled by decreasing IP.

In 1959, Karreman et al.[2] suggested that the striking pharmacological activity of LSD and related compounds may arise from the ability of these compounds to act as charge-transfer or electron-transfer donors at the active site(s). Since that time, this hypothesis has been supported by the observation of charge-transfer complexes involving various drugs and electron acceptors,[3] as well as by approximate quantum mechanical calculations of orbital energies,[4] which usually increase as the activity of the drug increases. Purported correlations between the calculated orbital energies of a drug and various types of biological activity have been variously supported or denied over the last decade.[1,4,5]

The experimental quantities most closely related to calculated orbital energies are the ionization potentials of molecules. Koopmans' theorem provides the theoretical, but approximate, connection between experimental ionization potentials (IP's) and SCF-calculated molecular orbital energies (ϵ^{SCF}): $IP_i = -\epsilon_i^{SCF}$.[6] All calculations performed on molecules of moderate size are, of necessity, approximate, and, in any case, Koopmans' theorem is known to be deficient, especially in cases where orbitals of different types are compared. Photoelectron spectroscopy measures experimental ionization potentials of isolated molecules in the gas phase, where there is no interference from solvation and steric effects inherent in charge-transfer complexation studies. We report here the photoelectron spectrum of LSD and show how the experimental ionization potentials of this molecule are, indeed, lower than those of certain analogous, but less active, tryptamine and phenethylamine derivatives whose photoelectron spectra we have reported elsewhere.[7]

The photoelectron spectrum of LSD is shown in Figure 1, along with that of the simpler hallucinogenic analogue, *N,N*-dimethyltryptamine (DMT). Attempts to run lysergic acid amide and isolysergic acid amide were not successful because both samples underwent extensive decomposition at the elevated temperatures necessary for volatilization in our spectrometer. The spectra were recorded on a Perkin-Elmer PS-18 photoelectron spectrometer with He(I) source; the measurements were carried out on the molecules in the gas phase at elevated temperatures using xenon and argon as internal calibrants. To enable assignment of the various bands to ionizations arising from orbitals on the indole, tertiary amine, or amide moieties, we compare, in Figure 2, the vertical ionization potentials observed for LSD with those of models for the indole (*N,N*-dimethyltryptamine), tertiary amine and alkene (*N*-methyl-1,2,5,6-tetrahydropyridine), and amide (*N,N*-diethylisobutyramide) moieties present in LSD.

The lowest three π ionization potentials of *N,N*-dimethyltryptamine occur at 7.57, 8.22, and 9.54 eV, while the tertiary amine lone pair gives rise to an unresolved ionization near 8 eV.[7] An isolated trisubstituted alkene such as the 9,10 double bond in LSD would have an ionization potential of less than 9.37 eV, the value of the π IP of 1,2,5,6-tetrahydro-*N*-methylpyridine.[8] Conjugation of this π orbital with the π orbitals of the indole moiety of tryptamine will be appreciable, since these π systems are mutually twisted by only 11° in LSD.[9] This conjugation will have a relatively large effect on the lowest two DMT-like π ionization potentials, which arise from orbitals, π_1 and π_2, that are higher in energy than the trisubstituted alkene orbital. Thus, mixing of π_1 and π_2 with the alkene orbital will cause a destabilization of the two highest indole orbitals and a stabilization of the alkene orbital.[10] The mixing of the alkene π orbital with the third π orbital of the indole moiety will destabilize the alkene orbital and stabilize π_3. As shown in Figure 2, these considerations lead to assignment of the 7.25 ± 0.10, 8.04 ± 0.12, 8.54 ± 0.09, and 9.75 ± 0.10 eV ionization potentials to those arising from the orbitals of the 4-vinylindole π system. Three other low-energy ionizations are expected in the 7–9 eV regions of the spectrum. The tertiary amine lone pair ionization will be similar to that in the tetrahydropyridine model (8.67 eV).[8] This ionization must be in the intense region around 8.4 eV, which contains several ionization bands. *N,N*-Dimethylisobutyramide has carbonyl–nitrogen (π_{NCO}) and oxygen (n_O) ionization potentials of 8.80 and 9.14 eV, respectively. The former type is un-

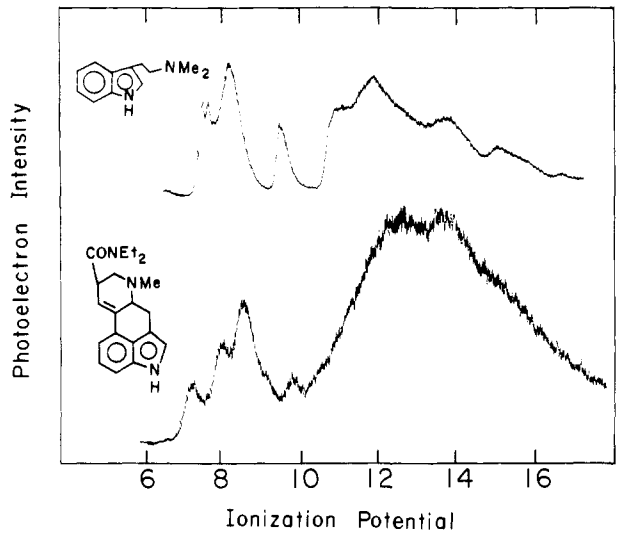

Figure 1. The photoelectron spectra of *N,N*-dimethyltryptamine and lysergic acid diethylamide.

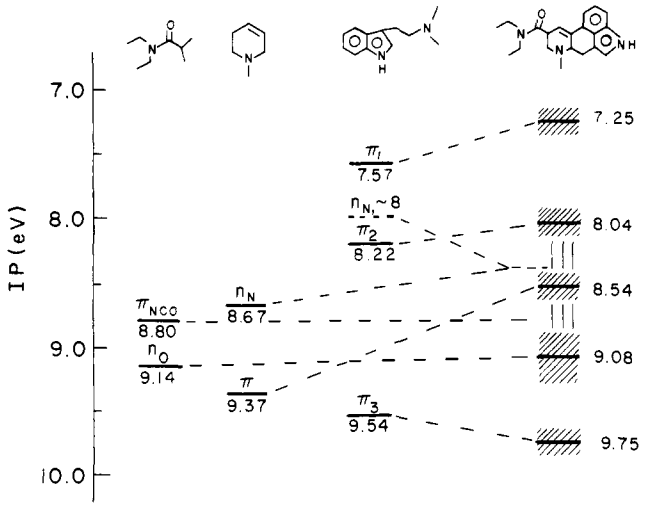

Figure 2. Ionization potentials of lysergic acid diethylamide and model compounds.

doubtedly in the unresolved 8.5–9.0-eV region of the LSD spectrum while the latter is assigned to the 9.08 ± 0.02 eV shoulder in the LSD spectrum.

The lowest π ionization potential of LSD (7.25 eV) is significantly lower than that of *N,N*-dimethyltryptamine (7.57 eV) and other substituted tryptamines we have studied.[7] Nevertheless, the first ionization potential of LSD is not abnormally low as compared to other good electron donors, such as phenothiazines and related neuroleptics. For example, promazines have IP's of 7.1–7.3 eV.[11] However, some support for the hypothesis that electron-donor ability is related to behavioral activity may be found from the comparisons described below.

Hallucinogenic activities of LSD and related compounds are frequently measured in terms of dosage data which, unfortunately, do not indicate the amount of drug required at the active site for activity. Substituents on a drug which appear to enhance its activity by increasing its metabolic stability, absorption, or transport to the active site may exert detrimental electronic or steric effects at the active site and thus limit its inherent activity. Vogel and Evans have recently reported rat behavioral data including activities of most of the compounds we have studied. Part of the difficulties mentioned above are overcome, because the concentration of the drug present in the rat brain at onset of behavioral effects has been measured.[12] The data

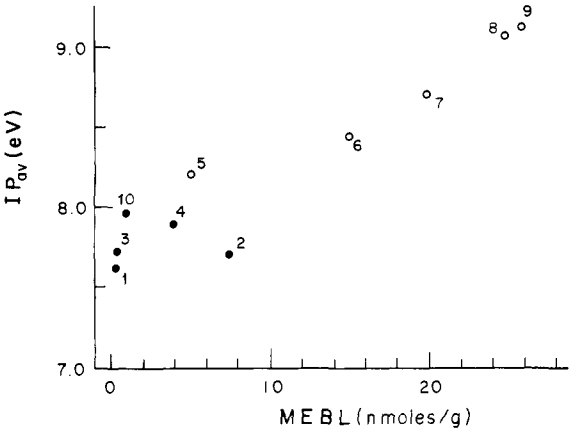

Figure 3. Plot of average of the first two π ionization potentials (IP_{av}) of hallucinogens and related compounds vs. the minimum effective brain level (MEBL) to alter rat behavior in a conditioned avoidance response (1 = LSD; 2 = 5-methoxydimethyltryptamine; 3 = 5-methoxytryptamine; 4 = dimethyltryptamine; 5 = mescaline; 6 = 3,4-dimethoxyphenethylamine; 7 = 4-methoxyphenethylamine; 8 = amphetamine; 9 = phenethylamine; 10 = tryptamine after MAO inhibition; ● = tryptamine derivatives; ○ = phenethylamine derivatives).

are for minimal effective brain levels (MEBL's) to interfere with the conditioned avoidance response of rats in a shuttlebox. These data are expected to reflect the intrinsic potency of a drug, more or less uncomplicated by absorption, transport, and metabolic differences. However, the behavioral effect measured is rather nonspecific, and a variety of active sites, as well as nonspecific binding, could be involved in the disruption of the conditioned avoidance response in the rat. However, the potencies in this test correlate roughly with measurements of hallucinogenic potency in man and may provide an animal model for hallucinogenicity. Figure 3 shows a plot of Vogel's minimum effective brain level (MEBL) to cause behavioral alterations in rats vs. the average of the first and second ionization potentials, IP_{av}, we have measured for several phenethylamines and tryptamines[7] and for LSD. This average is used to reflect more accurately the inherent electron-donor ability of the molecule than is indicated by the first IP alone.[7] That is, for five of the compounds in Figure 3 (5-methoxytryptamine, 5-methoxydimethyltryptamine, mescaline, phenethylamine, and amphetamine), the first and second IP's are separated by less than 0.2 eV and these compounds are better donors than compounds with similar first, but much higher second, IP's. Indeed, in a more rigorous treatment of electron-donor ability, all of the ionization potentials of a molecule—to varying extents—must be taken into account, although generally only the lower ionization potentials will contribute significantly in determinations of donor ability.

The phenethylamines markedly increase in activity with an IP_{av} decrease, while the tryptamines studied so far have no dramatic internal correlation between activity and IP_{av}, although they are observed to scatter between the phenethylamine region and that of LSD. This scatter may be due, in part, to the metabolic instability of several of the tryptamines toward MAO; Vogel and Evans found that tryptamine itself (without MAO inhibition) was not detectable in the rat brain even at high dosages.[12] The tryptamines do, as a class, have lower IP_{av}'s and higher activities than the phenethylamines.

Although there are insufficient data at this time to establish a quantitative relationship between hallucinogenic activity and ionization potential, from Figure 3 we

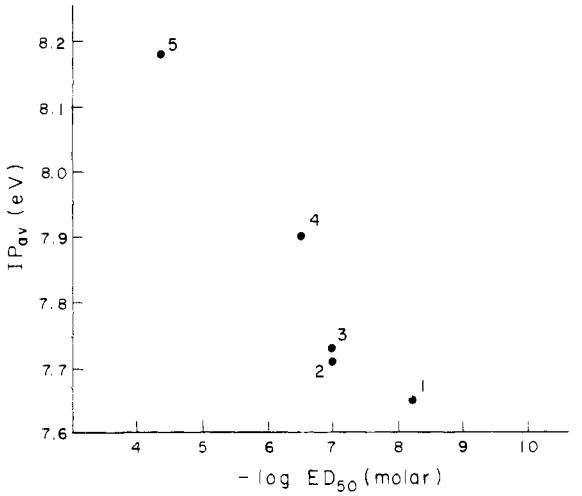

Figure 4. Plot of average of the first two π ionization potentials (IP_{av}) of hallucinogens and related compounds vs. their ability to displace specifically bound [^{3}H]-*d*-LSD in rat brain homogenates (-log ED_{50}) (1 = LSD; 2 = chlorpromazine; 3 = promethazine (IP's approximated from those of promazine); 4 = dimethyltryptamine; 5 = mescaline).

note that the drugs with low IP_{av}'s are recognized hallucinogens. For example, in terms of human dosage data, the relative hallucinogenic activities (and IP_{av}'s) of amphetamine, 4-methoxyphenethylamine, 3,4-dimethoxyphenethylamine, mescaline, 5-methoxy-*N*,*N*-dimethyltryptamine, and LSD are 0 (9.09 eV), <1 (8.68 eV), <0.2 (8.44 eV), 1 (8.18 eV), >31 (7.70 eV), and 3700 m.u. (7.64 eV), respectively.[7,13] A quantitative relationship between dosage measurements of hallucinogenic activity and a parameter which reflects electronic interactions at the active site, in this case IP_{av}, must involve, at the very minimum, a parameter, such as a partition coefficient, which reflects differences in transport of the agents to the active site. Such an analysis awaits the investigation of the photoelectron spectra of an extensive series of psychoactive drugs.

Figure 4 shows a plot of IP_{av} for several different types of psychotomimetic agents vs. their ability to displace specifically bound [^{3}H]-*d*-LSD in rat brain homogenates.[14] As in Figure 3, there is an emerging correlation between increasing activity and decreasing IP_{av}. Presumably, the ability of a molecule to displace LSD from its binding site stems from its ability to mimic the electronic interactions of LSD with the site. The size and detailed shape (topography) of the drug are also of crucial importance in determining activity, and correlations of activity with IP's for widely different structural types of hallucinogens are not to be expected.[4,5]

Although the receptor responsible for psychotomimetic activity, the mechanisms by which activity is induced, and the precise receptor morphology, particularly at the electronic level, are not yet known, evidence indicates that the phenethylamine class of drugs and the tryptamine class act by different mechanisms.[15] However, this preliminary investigation of the electronic structures of a variety of psychotomimetic agents indicates that the more active drugs are those with low IP_{av}'s. This correlation between increasing activity with decreasing ionization potential appears to hold for activity measured in conditioned avoidance response studies in rats, hallucinogenic activity studies in man, and LSD displacement studies in rat brain homogenates. Apparently for these types of activities, the ability of a drug to interact with a receptor is determined largely by its structural topography and by its ionization potential, which, in turn, is related to the ability of a compound to serve as a charge-transfer donor, through electrostatic, polarization, dispersion, and charge-transfer interactions.

Further studies of the electronic structures of a variety of drugs and their roles in determining activities are continuing in our laboratories.

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