using the procedure described for **2b**, to afford 0.93 g (2.1 mmol, 65.8% overall yield) of **3c**·oxalate, mp 148–150 °C. An analytical sample was recrystallized from benzene: mp 150–151 °C; $[\alpha]^{24}_D$ −19.8° (*c* 1.02, MeOH). Anal. ($C_{26}H_{35}NO_5$) C, H, N.

(−)-α-*N*-(Cyclopropylmethyl)-*N*-noracetylmethadol (2c). **3c**·oxalate (0.44 g, 1.0 mmol) was acetylated with Ac_2O, 0.44 g (4.3 mmol), in pyridine using the procedure of Eddy et al.;[18] the reaction workup is a modification of this procedure. The cooled reaction mixture was dissolved in Et_2O, and the Et_2O solution was washed with 0.1 N NaOH and H_2O. The Et_2O solution was dried over $MgSO_4$ and concentrated in vacuo, and the residue was heated at 40 °C in vacuo for 4.5 h. The residue was dissolved in Et_2O and converted to the oxalate salt, using the procedure described for **2b**, to afford **2c**·oxalate, 0.39 g (0.8 mmol, 80% yield): mp 208–209 °C; **2b**·HCl has $[\alpha]^{24}_D$ −20.3° (*c* 0.99, MeOH). Recrystallization of **2b**·oxalate from EtOAc afforded an analytical sample, mp 209–210 °C. Anal. ($C_{28}H_{37}NO_6$) C, H, N.

Preparation of HCl Salts. For biological testing, the HCl salts of **2b**, **2c**, **3b**, and **3c** were prepared by ion-pair extraction. In a typical experiment, 0.2 g (0.47 mmol) of **3b**·oxalate was dissolved in H_2O, the chilled solution was made alkaline with saturated $NaHCO_3$, and the liberated **3b** base was extracted into Et_2O. The Et_2O was collected, dried over $MgSO_4$, and concentrated in vacuo to afford **3b** as an oil. The oil was dissolved in 10 mL of 3 N HCl, and the acidic aqueous solution was extracted with $CHCl_3$ (5 × 20 mL), the $CHCl_3$ was collected, dried over $MgSO_4$, and concentrated in vacuo to afford 0.17 g (0.45 mmol, 95.7% crude yield) of **3b**·HCl as a hygroscopic glass.

Narcotic Analgesic and Antagonist Activity. Pharmacological screening for narcotic analgesic activity and analgesic antagonist activity was conducted by the Research Technology Branch, National Institute on Drug Abuse, using the mouse tail-flick, mouse acetic acid writhing, and mouse hot-plate assays. Swiss-Webster mice were used, and all drugs were administered by the subcutaneous route as the HCl salts. Narcotic antagonist activity was evaluated by determining the ability of the test compound to reverse mouse tail-flick analgesia induced by morphine sulfate (6.5 mg/kg, ED_{80}) administered 10 min before the test compound.

Opiate Receptor Binding Assay. Determination of stereospecific opiate receptor binding of the test compounds was conducted by Dr. Richard J. Miller of the University of Chicago. The ability of the test compounds to inhibit [^{3}H]naloxone binding to opiate receptors in rat brain membranes was measured using the procedure of Pasternak, Wilson, and Snyder.[19]

Acknowledgment. We thank Dr. Robert E. Willette, Research Technology Branch, National Institute on Drug Abuse, for furnishing (−)-α-acetylnormethadol hydrochloride and for performing the narcotic analgesic and analgesic antagonist studies. We thank Dr. Richard J. Miller, Department of Pharmacological and Physiological Sciences, the University of Chicago, for carrying out the opiate receptor binding assays. We thank Dr. Donald E. McMillan, Department of Pharmacology, University of Arkansas College of Medicine, for conducting the schedule-controlled pigeon behavior studies. This work was supported in part by a National Science Foundation Institutional Grant for Research (NSF-GU4226).

Studies on Phenethylamine Hallucinogens. 2. Conformations of Arylmethoxyl Groups Using ^{13}C NMR

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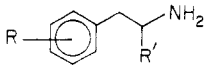
Carbon-13 chemical shift (δ) and spin–lattice relaxation time (T_1) measurements were used to determine the conformation around the Ar–OCH_3 bond of the arylmethoxyl groups in a series of substituted phenethylamines. Methoxyl groups flanked by two ortho substituents have δ ^{13}C values higher (60.5–62.5 ppm) than those with one or no ortho substituents (55.5–57.5 ppm) and T_1 values considerably longer than those of the other methoxyl groups in the same molecule. These measurements indicate that methoxyl groups with two ortho substituents acquire the out-of-plane conformation, while those with one or no ortho substitutents exist in the planar conformation. Phenethylamine analogues with methoxyl groups in the out-of-plane conformation have low or no psychotomimetic activity. A possible explanation is that the out-of-plane methoxyl group interferes with the binding of the *electron-rich* methoxy-substituted aromatic ring to a corresponding *electron-deficient* component on the active site of the receptor.

A large number of methoxyphenethylamine analogues have been synthesized[1,2] and evaluated in humans[3,4] and animals[5,6] for psychotomimetic activity. These compounds show drastic variations in psychotropic potency and are, thus, particularly suitable for studies in structure–activity relationships.



R = H, CH_3, OCH_3 or $-OCH_2O-$

R′ = H or CH_3

In previous studies[7,8] we have examined the role of α-alkyl substitution on the conformational properties of the side chain and the effects of conformation on the hallucinogenic activity of these compounds. The present study

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Table I. Carbon-13 Chemical Shifts and Spin-Lattice Relaxation Times[a] of Arylmethoxyl Carbons

$ArCH_2CHNH_2 \cdot HCl$ (R)

compd	Ar	R	OCH_3 δ	OCH_3 T_1, s	OCH_3 δ	OCH_3 T_1, s	OCH_3 δ	OCH_3 T_1, s
1	2-OCH_3	H	56.6	2.06				
2	4-OCH_3	CH_3	56.5	1.96				
3	2,5-$(OCH_3)_2$	CH_3	57.1	1.80	56.9	1.56		
4	2,4,5-$(OCH_3)_3$	CH_3	57.4	0.93	57.3	0.92	56.9	0.85
5	2,4,6-$(OCH_3)_3$	CH_3	56.4	0.92	56.4	0.92	56.4	0.92
6	2,5-$(OCH_3)_2$, 4-CH_3	CH_3	57.2	1.40	56.8	1.31		
7	3,4,5-$(OCH_3)_3$	H	57.1	1.20	*61.9*	*1.86*	57.1	1.20
8	3,4,5-$(OCH_3)_3$	CH_3	56.8	0.95	*61.6*	*1.44*	56.8	0.95
9	2,3,4-$(OCH_3)_3$	H	*62.2*	*3.44*	*61.7*	*3.14*	56.8	1.69
10	2,3,4-$(OCH_3)_3$	CH_3	*61.8*	*2.28*	*62*	*2.32*	56	1.39
11	2-OCH_3, 3,4-(OCH_2O)	H	*60.7*	*4.67*				
12[b]	2-OCH_3, 3,4-(OCH_2O)	CH_3	*60.7*					

[a] ±5%. [b] A limited amount of materials prevented the determination of T_1 values for this compound. The OCH_3 conformation should be identical with that of 11.

a – Planar Conformation (conjugated) b – Out of Plane Conformation (non-conjugated)

Figure 1.

deals with the effects associated with variations in the pattern of methoxyl group substitution in the aromatic ring. It is known that 2,5-dimethoxy substitution is generally associated with high psychotomimetic activity. For example, if the 3,4,5-trimethoxy substitution pattern in mescaline (7) is changed to a 2,4,5 orientation, there is an increase in psychotomimetic activity. On the other hand, 2,3,4-trimethoxy substitution results in analogues with no activity. However, if the 3- and 4-methoxyl substituents are exchanged with a 3,4-(methylenedioxy) group, activity is restored. Substitution of the 2-methoxyl with other groups is accompanied with a decrease (e.g., 2-SCH_3) or a total loss (e.g., 2-Br) of psychotomimetic activity.[9]

The important role that the aromatic methoxyl groups have on the potency of the psychotomimetic phenethylamines gives special importance to the conformational behavior of these groups in solution. Shulgin and coworkers[10] have suggested that the conformation of the individual methoxyl groups relative to the aromatic ring is one of the principal determinants of psychotomimetic activity. The conformations in question are those resulting from rotation around the Ar–OCH_3 bond. Arylmethoxyl groups can exist in one of two conformations (Figure 1). The first is a planar (a) conformation in which the O–CH_3 bond lies in the plane of the aromatic ring with the nonbonding oxygen electrons conjugated to the π system of the ring. The other is an out-of-plane (b) conformation with the O–CH_3 bond at right angles to the plane of the ring and the nonbonding oxygen electrons out of conjugation with the π cloud.

To date, the available information on the conformations of aromatic methoxyl groups in phenethylamines is limited to a very small number of analogues and comes mostly from theoretical calculations[11] and X-ray diffraction[11-13] studies. Photoelectron spectroscopy was used[14] to study such conformations in the gas phase. Domelsmith et al.[14] have demonstrated that in the gas phase, aromatic methoxyl groups reside in a planar conformation unless steric interactions from ortho substitution forces them into the less favored out-of-plane conformation. However, no such information is available for these molecules in solution.

Recently,[15] we have demonstrated the usefulness of ^{13}C chemical shifts and spin-lattice relaxation times (T_1) for the determination of arylmethoxyl group conformations in solution in a series of polymethoxy-substituted benzaldehydes and acetophenones. We showed that out-of-plane methoxyl groups have abnormally large ^{13}C chemical shifts and unusually long T_1 values. Following the same methods, we have now analyzed the methoxyl group conformations in a series of polymethoxyphenethylamines in solution and used the results to explain, at least in part, their relative hallucinogenic potencies.

Results

The methoxyl ^{13}C chemical shifts for the substituted phenethylamines studied here are given in Table I. In compounds 1–6 the methoxyl groups have either one or no ortho substituents and exhibit ^{13}C chemical shifts similar to that of *p*-methoxyamphetamine, suggesting a planar conformation. In contrast, compounds 7–12 have one or two methoxyl groups flanked by two ortho substituents. These methoxyl carbons exhibit ^{13}C chemical shifts 5–6 ppm downfield from *p*-methoxyamphetamine pointing to an out-of-plane conformation.[15] Table II lists the corresponding ^{13}C spin-lattice relaxation times. With molecules of intermediate size, such as substituted phenethylamines, spin-lattice relaxation is dominated by the ^{13}C–^{1}H dipole–dipole mechanism.[16,17] As a result of this, an increase

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Table II. Aromatic Methoxyl Group Conformations and Psychotomimetic Activity

compd	Ar	conformation[a] H	OCH_3	OCH_3	OCH_3	psychotomimetic potency, MU[b]	ref
1	2-OCH_3	H	ip			c	
2	4-OCH_3	CH_3	ip			5	3
3	2,5-$(OCH_3)_2$	CH_3	ip	ip		8	3
4	2,4,5-$(OCH_3)_3$	CH_3	ip	ip	ip	17	3
5	2,4,6-$(OCH_3)_3$	CH_3	ip	ip	ip	10	3
6	2,5-$(OCH_3)_2$, 4-CH_3	CH_3	ip	ip		80	3
7	3,4,5-$(OCH_3)_3$	H	ip	op	ip	1	3
8	3,4,5-$(OCH_3)_3$	CH_3	ip	op	ip	2.2	3
9	2,3,4-$(OCH_3)_3$	H	op	op	ip	inact	26
10	2,3,4-$(OCH_3)_3$	CH_3	op	op	ip	inact	9
11	2-OCH_3, 3,4-(OCH_2O)	H	op			5	9
12	2-OCH_3, 3,4-(OCH_2O)	CH_3	op			10	3

[a] ip = in-plane conformation; op = out-of-plane conformation. [b] MU = mescaline units; effective dose of mescaline divided by the effective dose of compound evaluated in man (see ref 3). [c] Not tested.

in the rate of reorientation of the observed nucleus leads to less efficient relaxation and, therefore, longer T_1 values. Differences between methoxyl T_1 values within the same molecule would then reflect differences in the rates of rotation of these groups. As we have shown previously,[15] rotation around the O–CH_3 bond is restricted by the ortho protons when the methoxyl group exists in the planar conformation. In the out-of-plane conformation this restriction is eliminated, allowing for faster rotation and, consequently, longer T_1 values. ^{13}C spin–lattice relaxation time measurements are, thus, useful indicators of aryl-methoxyl conformational preference.

As seen in Table I, the methoxyl groups with abnormally large ^{13}C chemical shifts (60.7–62.2 ppm) also exhibited longer T_1 values as expected with groups existing in the out-of-plane conformation. The T_1 measurements confirm that compounds **7**, **8**, and **11** have one methoxyl group at right angles to the aromatic ring. We also find that methoxyl groups ortho to each other with no adjacent substituents exist in the planar conformation. These results differ from the previously reported conformational analysis based on gas-phase photoelectron spectroscopy[14,18] data where the authors conclude that one of the two methoxyl group lies out of the plane of the aromatic ring. The measurements also reveal that compounds **9** and **10** have two OCH_3 groups in the out-of-plane conformation on opposite sides of the aromatic ring. In each compound, both methoxyl carbons have large chemical shifts coupled with long T_1 values. These long T_1 values reflect free rotation around the O–CH_3 bond and indicate that the two groups in each molecule must lie out of the plane of the ring and away from each other. It is only through the additional information provided by the T_1 values that this last conclusion may be reached. Our results illustrate how the combination of ^{13}C chemical shifts and spin–lattice relaxation times can provide a good deal of detailed information on the conformational behavior of aromatic methoxyl groups.

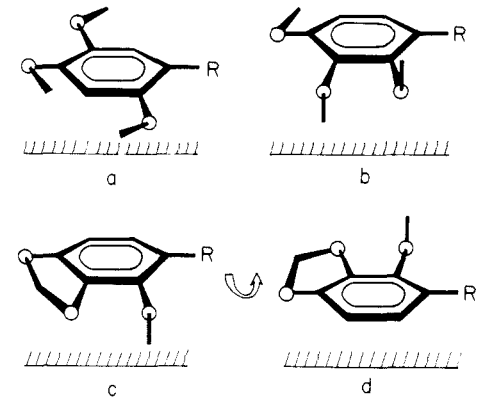

Figure 2.

Discussion

Table II compares the methoxyl group conformations in the series of substituted phenethylamines investigated here with their corresponding relative psychotomimetic activities. It can be seen that the compounds having one methoxyl group oriented out of the plane of the aromatic ring possess significantly less psychotomimetic activity compared to those that have all their methoxyl groups aligned with the plane of the ring. Compounds with two methoxyl groups perpendicular and on opposite sides of the ring (**9** and **10**) are devoid of psychotomimetic activity.

Snyder and Richelson[19] have suggested that the increase in psychotomimetic activity of the 2-methoxyl substituted phenethylamines is the result of hydrogen bonding between the aliphatic amine and the oxygen of the 2-OCH_3 group, thereby mimicking the middle portion of LSD. However, this hypothesis has not found substantial experimental support and fails to explain the low activity in the 2,3,4-trimethoxy substituted analogue. An alternative mechanism of drug–receptor interaction proposed by Szent-Györgi et al.[20] and elaborated by others[21,22] involves the formation of a complex between the electron-rich aromatic ring of the drug with an electron-deficient component of the receptor active site (Figure 2a). Under such a mechanism, the ability of the 2-methoxyl substitutent to enhance the psychotomimetic activity of the phenethylamines could be attributed to one or both of the

(17) With methyl groups undergoing rapid rotation, spin–rotation relaxation may have a significant contribution on the overall relaxation rate. The extent of this contribution may be determined by the measurement of the NOE for the methyl carbon. We measured the NOE's in **6**, a compound with the longest methoxyl ^{13}C T_1 values in the series and, consequently, the best candidate for a significant contribution from spin–rotation. We found no measurable contribution from the spin–rotation relaxation mechanism and concluded that, at least for the methoxyl carbons in the compounds studied here, the dipole–dipole mechanism is the only significant relaxation mechanism.

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following: (a) The electron density of the aromatic ring increases as a result of conjugation between the nonbonding electrons of the methoxyl oxygen and the π cloud of the aromatic ring. Such an increase would result in a stronger drug–receptor complex formation. (b) The 2-methoxyl nonbonding electrons are also directly involved in the interaction with the electron-deficient site at the receptor. This additional interaction enhances the affinity of the drug for the receptor.

The observed increase in psychotomimetic activity associated with the out-of-plane conformation can be explained by invoking steric hindrance from the methoxyl group during the approach of the drug to the receptor site. In the case of compounds with two methoxyl groups perpendicular and on opposite sides of the ring, the approach from either face of the aromatic ring to the receptor site is hindered (Figure 2b). This results in the loss of psychotomimetic activity. However, with the compounds that have one methoxyl group in the out-of-plane conformation, the approach of the drug to the receptor site is hindered only from one face of the ring (Figure 2c,d). This results only in a partial loss of psychotomimetic activity. It should also be pointed out that the methoxyl out-of-plane conformation decreases the electron density of the aromatic ring because the nonbonding oxygen electrons are no longer in conjunction with the π cloud. This should further decrease the affinity of these drugs toward the receptor.

We are currently investigating the electronic and steric implications resulting from the out-of-plane conformation of the aromatic methoxyl groups through the use of electron-deficient model receptor sites.[23]

Experimental Section

Samples for this work were provided by Dr. A. T. Shulgin and the National Institute on Drug Abuse. All chemical shifts and spin–lattice relaxation times were determined on a Bruker WP-60 NMR spectrometer equipped for pulse Fourier transform operation at 15.08 MHz. The system computer allows acquisition of 8K data points, thus yielding 4K data points in the transformed phase corrected spectrum. Samples were 0.75 M solutions of the hydrochloride salts in D_2O at 30 °C. Chemical shifts were determined using 5% dioxane as the internal standard (67.4 ppm downfield from Me_4Si).[24]

Spin–lattice relaxation times for all carbons directly attached to protons were determined simultaneously with complete proton decoupling using the $(180°-\tau-90°-T)_n$ inversion recovery method,[25] where τ is experimentally varied and T is equal to at least 5 times the longest T_1 to be measured. The T_1 calculations were performed on a Nicolet BNC-12 minicomputer using the Bruker T_1 Program/II, which estimates the T_1 values from peak intensities. Each reported T_1 value is the average of at least three determinations.

Heteronuclear nuclear Overhauser enhancement (NOE) measurements were carried out on a degassed sample using the method of Freeman et al.[27] A spectrum was first obtained with continuous broad-band proton decoupling. A second spectrum was then obtained using a pulse-modulated broad-band proton decoupling sequence. In this "gated" experiment, the decoupler is kept on only during data acquisition periods and is turned off during the remainder of the pulse interval. Proton-decoupled ^{13}C spectra are thus obtained without any appreciable NOE. Pulse intervals in both experiments were equal to at least 8 times the longest T_1. Values for the NOE were determined by dividing the individual peak area in the continuously decoupled spectrum with the corresponding peak area in the "gated" spectrum. The NOE sample was identical in every way with the sample used for T_1 measurements.

Acknowledgment. We thank Dr. A. T. Shulgin for the samples he generously provided and for the useful discussions on this work. This study was supported by a grant from the National Institute on Drug Abuse (NIDA-376) and a grant from the University of Connecticut Research Foundation (UCRF-257).

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Book Reviews

Encyclopedia of Chemical Technology. Third Edition. Volume 12. By Kirk-Othmer. Wiley, New York. 1980. xxvi + 1037 pp. 19 × 26 cm. $145.00.

This volume, as in the case of the previous volumes in this third edition, continues to provide chemists with an invaluable source of authoratative information on the many diverse topics of chemical technology. Of particular interest to medicinal chemists in Volume 12 are the excellent and up to date reviews of such topics as histamine and histamine antagonists (11 pages) by R. W. Fleming and J. M. Grisar. The 154-page discussion of hormones includes a survey (8 pages) by C. and J. Rivier, anterior-pituitary hormones (11 pages) by C. H. Li, anterior-pituitary-like hormones (6 pages) by H. Papkoff, posterior-pituitary hormones (11 pages) by A. F. Spatola, adrenal-cortical hormones (28 pages) by V. Petrow, brain oligopeptides (15 pages) by J. and C. Rivier, sex hormones (40 pages) by V. Petrow, and nonsteroidal estrogens (33 pages) by G. C. Crawley. In addition there is a 20-page discussion of hydantoin and derivatives by J. H. Bateman which includes all the medicinally used hydantoins and their physical properties, synthesis, and chemical properties. What makes these volumes particularly useful to chemists wishing to survey current technology is the inclusion of Chemical Abstracts Service registry numbers for all compounds. This is of considerable practical value for the chemist who wishes to further search the literature.

Staff

Instrumental HPTLC. Edited by W. Bertsch, S. Hara, R. E. Kaiser, and A. Zlatkis. Alfred Hüthig Verlag, Heidelberg and New York. 1980. 390 pp. 15 × 21 cm. $49.00.

This book, describing recent advances in high-performance thin-layer chromatography (HPTLC), is a collection of 16 papers presented at the First International Symposium on Instrumental HPTLC held in May 1980. Essentially two types of papers are included, those that emphasize the basic instrumental methods and chromatographic evaluation in HPTLC and papers detailing applications of HPTLC.