stirring at 25 °C under $N_2$ and stirred for 20 h, and the solid was filtered, washed with $CHCl_3$ (2 × 50 mL), and dried in vacuo at 50–55 °C. The resulting solid was dissolved in acetone (185 mL) at reflux temperature, treated with charcoal (1.29 g) at reflux temperature for 5 min, filtered through Supercel, diluted with $CHCl_3$ (185 mL), cooled, and stirred at 0–5 °C for 1 h. The resulting solid was filtered and dried in vacuo to afford 54.0 g (75.5%) of 1.

**Antifertility Test.** The sulfamates and methanesulfonic acid ester (Table I) were evaluated in a standard short-term antifertility test involving the oral administration of the test substance in propylene glycol to male Sprague–Dawley rats for 14 consecutive days prior to mating.[8] The males were then cohabitated with proestrus females, and the latter were autopsied 14 days after mating and examined for the status of pregnancy. Positive mating was confirmed by sperm in vaginal washings. After cohabitation, all males were autopsied for examination of the testes, epididymides, and accessory sex organs. Portions of the testes and epididymides from the rats that received compound 1 at 0.68 mmol/kg were fixed in neutral formalin and subsequently embedded, sectioned, mounted, and stained with hematoxylin–eosin according to standard histological procedures.

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# Synthesis of Analogues of Acetylmethadol and Methadol as Potential Narcotic Antagonists

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The *N*-allyl and *N*-(cyclopropylmethyl) analogues of (-)-α-acetylmethadol and (-)-α-methadol have been synthesized and evaluated for opiate agonist and opiate antagonist activity. Both acetylmethadol analogues possessed weak analgesic activity in in vivo tests for narcotic analgesia; the *N*-allyl analogue partially antagonized morphine-induced tail-flick analgesia. All four compounds possessed only opiate agonist-like activity as determined by in vitro studies measuring inhibition of [$^3$H]naloxone binding to opiate receptors.

Opiate antagonists are generally derived from opiate agonists by replacing the methyl group on the tertiary amine with an appropriate antagonist pharmacophore, e.g., allyl, dimethylallyl, cyclopropylmethyl, or cyclobutylmethyl.[1,2] All the clinically useful opiate antagonists have been obtained by structural modification of opiate analgesics that have fused ring systems, such as morphinoids, morphinans, or benzomorphans. With the exception of naloxone and naltrexone, which are "pure" narcotic antagonists derived from oxymorphone, all these agents possess both opiate agonist and opiate antagonist properties and are classified as opiate agonist–antagonists or partial agonists.

Opiate antagonists have also been derived from opiate agonists not possessing fused rings. Although no narcotic antagonist activity was reported for analogues of meperidine,[3-6] Oh-ishi and May[7] found that the *N*-hexyl and *N*-heptyl derivatives of norketobemidone were partial agonists with antagonist activity on the order of that of pentazocine. More recently, Zimmerman et al.[8] reported a series of 3,4-dimethyl-4-phenylpiperidines that are pure narcotic antagonists. The most potent pure antagonist in the series is the (+)-*N*-(2-propiophenone) derivative which has activity equal to that of naloxone. Iorio and Casy[9,10] observed that the *N*-allyl and *N*-(cyclopropylmethyl) derivatives of 2,3-dimethyl-3-(3-hydroxyphenyl)piperidine were pure narcotic antagonists with antagonist activity similar to that of nalorphine.

Jacoby and colleagues[11] found no narcotic antagonist activity in a series of N-substituted 3-phenylpyrrolidines. However, Bowman et al.[12] reported mixed agonist–antagonist activity for *N*-alkyl derivatives of 3-(3-hydroxyphenyl)pyrrolidines. In compounds derived from bicyclic systems, Ong and co-workers[13] observed opiate agonist–antagonist activity in *N*-alkyl-5-aryl-2-azabicyclo[3.2.1]-octanes. Clarke et al.[14] synthesized pure narcotic antagonists utilizing 2-phenyl- and 2-(3-hydroxyphenyl)tropanes.

The apparent requirement of a phenolic hydroxyl group for opiate antagonist activity must not be overlooked. With few exceptions, all the compounds noted above that exhibit either partial agonist or pure antagonist activity also possess a phenolic hydroxyl group. The exceptions involve some of the tropane derivatives having opiate antagonist activity synthesized by Clarke and co-workers;[14]

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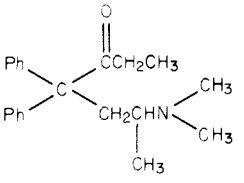
however, the most potent antagonists in this series do possess phenolic hydroxyl substituents.

There are no reports of attempts to synthesize narcotic antagonists derived from the methadone (1) series of analgesics (methadone, methadol, and acetylmethadol). Although this series of opiates possesses a tertiary nitrogen that is not part of a heterocyclic ring, there is precedence for narcotic antagonist activity for compounds in which the amine nitrogen is acyclic. The $S_2$ isomer of viminol, 1-[$\alpha$-(*N*-*o*-chlorobenzyl)pyrrolyl]-2-(*R*,*R*)-di-*sec*-butylamino-(1*S*)-ethanol, has been reported to antagonize the analgesic effect of morphine.[15]

The methadone series of narcotic agonists serves as excellent models to study the structural and stereochemical requirements for narcotic antagonist activity. The compounds in this series are structurally and stereochemically less complex than the fused-ring polycyclic opiates, and the absolute configuration has been determined for all the stereoisomers.[16,17] Inasmuch as the tertiary nitrogen is acyclic, the series lends itself readily to substitution of two antagonist pharmacophoric groups at the nitrogen.

In an effort to further elucidate the structural and stereochemical requirements for narcotic antagonists, we have synthesized a number of *N*-alkyl analogues of acetylnormethadol (**2a**) and normethadol (**3a**). We report the synthesis and preliminary pharmacological activity of the first compounds (**2b**,**c** and **3b**,**c**) of this series.



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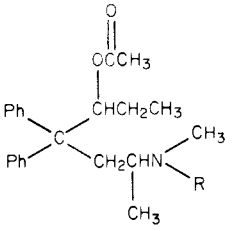
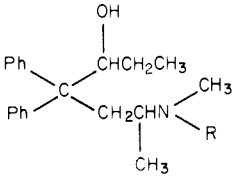


**2a**, R = H
**b**, R = $CH_2CH{=}CH_2$
**c**, R = $CH_2$-c-Pr
**d**, R = CO-c-Pr

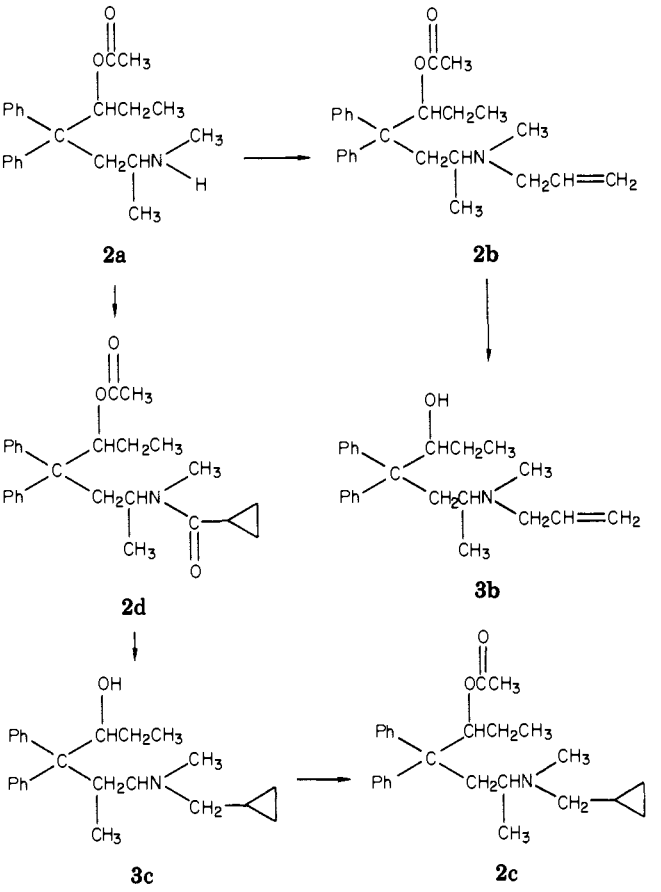


**3a**, R = H
**b**, R = $CH_2CH{=}CH_2$
**c**, R = $CH_2$-c-Pr

**Chemistry.** Scheme I shows the synthetic schemes used for the synthesis of both the acetylnormethadol analogues (**2b**,**c**) and normethadol analogues (**3b**,**c**). These are all straightforward reactions chosen to maintain the integrity of the chiral centers in the starting material, (−)-$\alpha$-acetyl-*N*-normethadol (**2a**).

(−)-$\alpha$-*N*-Allyl-*N*-noracetylmethadol (**2b**) was synthesized by alkylation of **2a** using 3-bromopropene (allyl bromide). Alkaline hydrolysis of **2b** afforded (−)-$\alpha$-*N*-allyl-*N*-normethadol (**3b**). The *N*-(cyclopropylmethyl) analogues (**2c** and **3c**) were synthesized by first treating **2a** with cyclopropanecarboxylic acid chloride. The crude amide **2d** was reduced with sodium bis(2-methoxyethoxy)aluminum dihydride to afford (−)-$\alpha$-*N*-(cyclopropylmethyl)-*N*-normethadol (**3c**). The alcohol **3c** was acetylated according to the procedure of Eddy et al.[18] to afford (−)-$\alpha$-*N*-(cyclopropylmethyl)-*N*-noracetylmethadol (**2c**). All the desired compounds were isolated, purified, and analyzed as the oxalate salts. In our hands, the hydrochloride salts were either difficult to crystallize or crystallized in poor yields. Hydrochloride salts were prepared by ion-pair extraction in sufficient quantities for biological evaluation.

Scheme I



**2a** **2b** **2d** **3b** **3c** **2c**

Table I. Narcotic Analgesia and Analgesic Antagonist Activity of *N*-Alkyl Analogues of (−)-$\alpha$-Acetyl-*N*-normethadol

| | $ED_{50}$,[a] mg/kg | | |
|---|---|---|---|
| analgesic test | **2b**[b] | **2c**[b] | morphine[b] |
| tail flick | 3.1 (1.0-4.3) | weak up to 30[d] | 3.3 (1.9-5.8) |
| hot plate | 10.0 (4.7-21.0) | | 3.05 (1.3-6.75) |
| writhing | 2.5 (0.57-11.7) | inact at 30 | 0.82 (0.34-1.97) |
| antagonism of tail-flick analgesia[c] | 61.4% at 1 mg/kg | inact at 10 | |
| | 56.9% at 0.3 mg/kg | | |

[a] 95% confidence limits in parentheses. [b] Compounds **2b** and **2c** as HCl salts; morphine sulfate. [c] Tail-flick analgesia induced by 6.5 mg/kg of morphine sulfate ($ED_{80}$). [d] 38% analgesia at 30 mg/kg.

## Biological Results

The *N*-allyl (**2b**) and *N*-(cyclopropylmethyl) (**2c**) derivatives of (−)-$\alpha$-acetyl-*N*-normethadol were evaluated for narcotic analgesic and analgesic antagonist activity in mice, and the results are shown in Table I. The *N*-allyl deriv-

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Table II. Inhibition of [$^3$H]Naloxone Opiate Receptor Binding by *N*-Alkyl Derivatives of (−)-α-Acetylnormethadol and (−)-α-Normethadol and by Other Methadone, Methadol, and Acetylmethadol Stereoisomers

| compd | $K_i$, M | |
|---|---|---|
| | no $Na^+$ | 100 mM $Na^+$ |
| **2b**[a] | $9 \times 10^{-7}$ | $1 \times 10^{-5}$ |
| **2c**[a] | $2 \times 10^{-6}$ | $3 \times 10^{-5}$ |
| **3b**[a] | $1.5 \times 10^{-7}$ | $2 \times 10^{-6}$ |
| **3c**[a] | $6 \times 10^{-7}$ | $5 \times 10^{-6}$ |
| (−)-(6*R*)-methadone[b] | $2 \times 10^{-9}$ | $7.7 \times 10^{-8}$ |
| (+)-(6*S*)-methadone[b] | $1.1 \times 10^{-7}$ | $3.2 \times 10^{-6}$ |
| (−)-α-(3*S*,6*S*)-methadol[b] | $1.1 \times 10^{-6}$ | $6.8 \times 10^{-6}$ |
| (+)-α-(3*R*,6*R*)-methadol[b] | $2.3 \times 10^{-7}$ | $2.3 \times 10^{-7}$ |
| (−)-α-(3*S*,6*S*)-acetylmethadol[b] | $1.5 \times 10^{-8}$ | $4.5 \times 10^{-7}$ |
| (+)-α-(3*R*,6*R*)-acetylmethadol[b] | $1.2 \times 10^{-9}$ | $3.4 \times 10^{-9}$ |
| morphine sulfate | $6.0 \times 10^{-9}$ | $1.9 \times 10^{-7}$ |

[a] Tested as HCl salts (see ref 19); three replicate experiments ($n = 3$) for each $K_i$. [b] $K_i$ calculated from data in ref 20.

ative (**2b**) possesses modest analgesic activity in all three models for opiate analgesia. The *N*-(cyclopropylmethyl) derivative (**2c**) was evaluated only in the tail-flick and writhing assays; the compound had only weak analgesic activity in the tail-flick model and was inactive in the writhing assay. Only **2b** demonstrated narcotic antagonist activity as measured by its ability to reverse mouse tail-flick analgesia induced by morphine. The compound antagonized morphine-induced analgesia by 61.4 and 56.9% at doses of 1 and 0.3 mg/kg, respectively.

The opiate receptor binding of compounds **2b**, **2c**, **3b**, and **3c** was determined using rat brain membranes according to the procedure of Pasternak, Wilson, and Snyder.[19] The binding data are shown in Table II. Both *N*-alkyl derivatives (**2b,c**) of (−)-α-acetyl-*N*-normethadol are less potent than (−)- and (+)-α-acetylmethadol in preventing naloxone binding. Furthermore, the (−)-α-acetyl-*N*-normethadol derivatives are less potent in this respect than the *N*-alkyl derivatives (**3b,c**) of (−)-α-*N*-normethadol. Both **3b** and **3c** have potency on the order of (+)-α-methadol, which is the most potent α-methadol antipode that inhibits naloxone receptor binding.[20] The inhibition of naloxone receptor binding by **2b**, **2c**, **3b**, and **3c** is decreased in the presence of $Na^+$ which is typical for opiate agonists.

Compounds **2b**, **2c**, **3b**, and **3c** were also studied for their effects on the schedule-controlled behavior of the pigeon.[21] In this regard, all four compounds possess methadone-like effect on schedule-controlled behavior. The effects of all four compounds are reversed by naloxone, and none of the compounds produce opiate antagonist activity in this behavior model.

## Conclusions

The preliminary biological activity of these *N*-alkyl analogues of acetylmethadol and methadol indicates that these compounds possess only opiate agonist activity. Although **2b** appears to have weak antagonist activity in the mouse tail-flick assay, the naloxone binding inhibitory potency decreases in the presence of $Na^+$, and it possesses no opiate antagonist properties in the pigeon behavior model.

Inasmuch as **2b**, **2c**, **3b**, and **3c** are all synthesized from (−)-α-(3*S*,6*S*)-acetylnormethadol, these compounds all have the 3*S*,6*S* configuration. The acetylmethadol stereoisomer having the greatest analgesic potency possesses the 3*S*,6*R* configuration; the most potent methadol stereoisomer possesses the 3*S*,6*S* configuration.[17] Thus, **3b** and **3c** represent the most likely candidates for methadol analogues having narcotic antagonist activity. However, the naloxone binding inhibition studies and data from the pigeon behavior model indicate that the compounds possess only opiate agonist activity.

## Experimental Section

Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded as KBr pellets using a Beckman Acculab IV infrared spectrophotometer. Spectral data were consistent with the assigned structures in all cases. Optical rotations were determined using a Perkin-Elmer Model 241 polarimeter. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. The (−)-α-acetyl-*N*-normethadol was graciously furnished by the Research Technology Branch, National Institute on Drug Abuse.

**(−)-α-*N*-Allyl-*N*-noracetylmethadol (2b).** An aqueous solution of 1.2 g (3.2 mmol) of **2a**·HCl was cooled in an ice bath, made alkaline with concentrated $NH_4OH$, and extracted with $Et_2O$. The $Et_2O$ was collected, dried over $Na_2SO_4$, and concentrated in vacuo to afford the free base, **2a**, in quantitative yield. A solution of **2a** in 30 mL of 2-propanol was added dropwise with stirring to a refluxing solution of 0.41 g (3.4 mmol) 3-bromopropene in 2-propanol over 1.2 g of $K_2CO_3$. The reaction mixture was heated at reflux overnight, cooled, filtered, and concentrated in vacuo to afford an oily product which was dissolved in $Et_2O$. The $Et_2O$ solution was extracted with 0.1 N HCl; the HCl solution was collected, made alkaline with 0.1 N NaOH, and extracted with $Et_2O$. The $Et_2O$ was collected, dried over $Na_2SO_4$, and concentrated in vacuo to afford 1.03 g (2.7 mmol, 84.4% crude yield) of **2b** as a thick oil. Crude **2b** was dissolved in $Et_2O$, and the oxalate salt was prepared by the addition of a saturated solution of ethereal oxalic acid. Filtration afforded 1.2 g (2.6 mmol, 81.2% yield) of **2b**·oxalate, mp 190–193 °C. Recrystallization from acetone afforded an analytical sample: mp 191–193 °C; $[\alpha]^{24}_D$ −31.3° (*c* 1, MeOH). Anal. ($C_{27}H_{35}NO_6$) C, H, N.

**(−)-α-*N*-Allyl-*N*-normethadol (3b).** A solution of 1.05 g (2.2 mmol) of **2b**·oxalate in MeOH was added to a solution of 3.08 g (54.9 mmol) of KOH in MeOH and heated at reflux for 17 h. The reaction mixture was concentrated in vacuo, dissolved in $H_2O$, and extracted with $Et_2O$; the $Et_2O$ was collected, dried over $Na_2SO_4$, and concentrated in vacuo to afford **3b** as a thick yellow oil. The oxalate salt was prepared as for **2b** to afford 0.72 g (1.7 mmol, 77.3% yield) of **3b**·oxalate, mp 134–136 °C. Recrystallization from benzene afforded an analytical sample: mp 138–139 °C; $[\alpha]^{24}_D$ −14.1° (*c*, 1.01, MeOH). Anal. ($C_{25}H_{33}NO_5$) C, H, N.

**(−)-α-*N*-(Cyclopropylcarbonyl)-*N*-noracetylmethadol (2d).** A solution of **2a**, prepared from 0.56 g (1.5 mmol) of **2a**·HCl according to the procedure used for **2b**, in dry benzene (Na metal) was added dropwise with stirring to a refluxing mixture of 0.19 g (1.8 mmol) of cyclopropanecarboxylic acid chloride and 0.76 g of $K_2CO_3$ in dry benzene. After refluxing for 1 h, an additional 0.19 g (1.8 mmol) of acid chloride was added, and the mixture was heated at reflux overnight. The reaction mixture was cooled and filtered, and the filtrate was washed with 1 N HCl, 1 N NaOH, and $H_2O$. The benzene solution was dried ($MgSO_4$) and concentrated in vacuo to afford crude **2d** in quantitative yield; this product was not purified further for use in subsequent reactions.

**(−)-α-*N*-(Cyclopropylmethyl)-*N*-normethadol (3c).** Crude **2d** (1.29 g, 3.2 mmol) in dry benzene (Na metal) was added dropwise with stirring to a solution of 14.4 mmol (4.25 mL of a 70% solution in benzene) of sodium bis(2-methoxyethoxy)aluminum dihydride in dry benzene under $N_2$. The reaction mixture was heated at reflux for 30 min, cooled to room temperature, and worked up in the usual manner to afford 0.880 g (2.5 mmol, 78.1% yield) of crude **3c** as an oil; this was converted to the oxalate salt,

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(21) D. E. McMillan, D. L. Lattin, W. C. Hardwick, D. L. Greene, P. K. Raible, and J. B. Richardson, unpublished results.

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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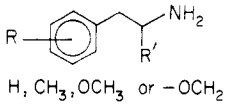
Carbon-13 chemical shift (δ) and spin–lattice relaxation time ($T_1$) measurements were used to determine the conformation around the Ar–$OCH_3$ bond of the arylmethoxyl groups in a series of substituted phenethylamines. Methoxyl groups flanked by two ortho substituents have δ $^{13}$C values higher (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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