**Acknowledgment.** We wish to express our appreciation to Dr. G. Ullyott of Smith Kline & French Laboratories who provided us with **1a** and **1b** for this study.

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# Importance of the Aromatic Ring[1] in Adrenergic Amines. 2. Synthesis and Adrenergic Activity of Some Nonaromatic Six- and Eight-Membered Ring Analogs of β-Phenylethanolamine[2,3,†]

Gary L. Grunewald,* Joseph M. Grindel,

*Department of Medicinal Chemistry, School of Pharmacy, The University of Kansas, Lawrence, Kansas 66045*

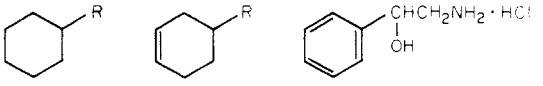
Popat N. Patil, and Kadhim N. Salman

*Division of Pharmacology, College of Pharmacy, The Ohio State University, Columbus, Ohio 43210.* *Received May 30, 1975*

The synthesis of β-phenylethanolamine analogs in which the phenyl ring is replaced by cyclohexyl, cyclohexen-4-yl, cyclooctyl, cyclooctenyl, cycloocta-1,3-dien-2-yl, cycloocta-1,5-dienyl, and cyclooctatetraenyl was accomplished by conversion of the corresponding aldehydes to the cyanohydrins followed by reduction with lithium aluminum hydride. A preparatively useful synthesis of 1-formylcyclooctatetraene is described utilizing the photocycloaddition of methyl propiolate to benzene followed by reduction to the alcohol and oxidation with $MnO_2$. All compounds, as their hydrochloride salts, exhibited indirect adrenergic activity on the rat vas deferens. On the reserpinized rat vas deferens all compounds potentiated the effects of exogenous norepinephrine. The results are in agreement with the conclusion that the more saturated the ring moiety, the greater the affinity for the amine uptake site of the vas deferens and suggest that there is no important interaction between the drug and this uptake site that involves π-complex formation.

The presence of an aromatic ring in a variety of drug molecules has led to speculations regarding the contribution of interactions between the aromatic ring and the pharmacological site of action to the overall observed pharmacological activity of the given drug. In the case of adrenergic amines and the α-adrenergic receptor site, an interaction between the electron-rich π cloud of the aromatic ring and an electron-deficient area of the receptor has been suggested in a number of theories and receptor models.[4-7]

In this paper we shall describe the synthesis and preliminary adrenergic evaluation of two series of β-phenylethanolamine analogs in which there is a varying degree of ring unsaturation. The first series of six-membered ring analogs of β-phenylethanolamine (**3**) consists of the fully saturated cyclohexylethanolamine (**1a**), the partially saturated cyclohexen-4-ylethanolamine (**2a**), and the parent aromatic β-phenylethanolamine (**3**).



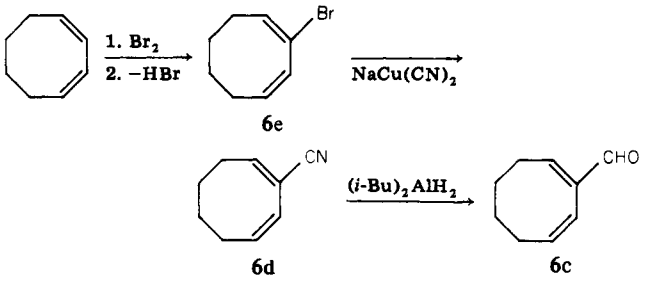

1 2 3

**a**, R = $CH(OH)CH_2NH_2 \cdot HCl$
**b**, R = CH(OH)CN
**c**, R = CHO

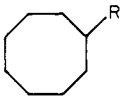
The second series consists of eight-membered ring analogs of **3** and ranges from the fully saturated cyclooctylethanolamine (**4a**), through the monounsaturated cyclooctenylethanolamine (**5a**), to more unsaturated derivatives, cycloocta-1,3-dien-2-ylethanolamine (**6a**) and cycloocta-1,5-dienylethanolamine (**7a**), and to the fully

† This paper is dedicated to the memory of Edward E. Smissman, a trusted friend whose inspiration and encouragement will not be forgotten.

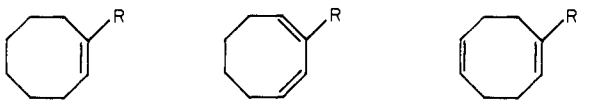
Scheme I




unsaturated cyclooctatetraenylethanolamine (8a).

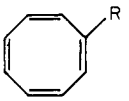


4a, R = $CH(OH)CH_2NH_2 \cdot HCl$
b, R = CH(OH)CN
c, R = CHO



5 6 7

a, R = $CH(OH)CH_2NH_2 \cdot HCl$
b, R = CH(OH)CN
c, R = CHO
d, R = CN
e, R = Br



8a, R = $CH(OH)CH_2NH_2 \cdot HCl$
b, R = CH(OH)CN
c, R = CHO
d, R = $CH_2OH$
e, R = $COOCH_3$

In the six-membered series we have the aromatic parent (3) and the more lipophilic derivatives **2a** and **1a**, in which the ability of the ring moieties to participate in π-complex formation is severely reduced (**2a**) or absent (**1a**). To minimize the problem of having an aromatic ring compound as a member of the series and to minimize the effects of conformational changes in the ring moieties of a given series, we also prepared the set of eight-membered ring compounds in which none of the members has a planar ring system and none is aromatic. There is a more gradual change in π character of the rings than in the six-membered series in going from the fully saturated **4a** to the fully unsaturated cyclooctatetraenyl derivative **8a**. If π-complex formation is an important factor in activity of adrenergic amines, the unsaturated derivative (**8a**) should be the most active member of the series. The cyclooctadiene analogs (**6a** and **7a**) retain a significant ability to participate in π-complex formation. This property is greatly reduced in the cyclooctene derivative (**5a**) and absent in the saturated cyclooctane derivative (**4a**). There would still be subtle differences in conformation and "ring shape" among members of this series, but the changes would not be as drastic as produced in going from **1a** to **3**.

In our previous paper[1] we noted that π complexation between the ring moiety and the active site of phenylethanolamine *N*-methyltransferase (PNMT) was not a necessity for good substrate activity, and, in fact, the nonaromatic cyclooctyl analog **4a** was an excellent substrate for this enzyme when compared to β-phenylethanolamine (**3**) (vida infra). We were thus interested in investigating the activity of these nonaromatic derivatives at other adrenergic sites, particularly in light of the earlier observation of Iversen[8] that an aromatic ring was not essential for inhibition of the uptake$_1$ mechanism of the isolated rat heart. They observed, for example, that propylhexedrine (2-methylamino-1-cyclohexylpropane) was more potent than β-phenylethylamine at binding at the uptake$_1$ site. However, they studied only fully aromatic or fully saturated analogs. For our studies, we chose initially to look at peripheral activity on the isolated rat vas deferens.

Table I. Dehydrohalogenation Procedures and Yields for Vinyl Bromides

| Compd | LiCl[a] | *t*-BuOK[b] | $Et_2NH$[c] | KOH[d] | DBU[e,f] |
|---|---|---|---|---|---|
| 5e | 23% | 43% | 40% | 39% | 36% |
| 6e | | | | 53% | 45% |
| 7e | 20% | | 6% | 25% | 31% |

[a] E. W. Warnhoff, D. G. Martin, and W. S. Johnson, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 162. [b] Reference 17. [c] Reference 18. [d] Reference 20. [e] Reference 21. [f] 1,5-Diazabicyclo[4.3.0]undec-5-ene.

Table II. A Comparison of the Uv $\lambda_{max}$ of the 2,4-DNP[a] Derivatives of Compounds 5c and 6c[b]

| Compound | Calcd[c] $\lambda_{max}$, nm | Exptl $\lambda_{max}$, nm |
|---|---|---|
| 5c·2,4-DNP | 379 | 378 |
| 6c·2,4-DNP | 384 | 385 |
| 1-Formylcycloocta-1,3-diene·2,4-DNP | 415 | |

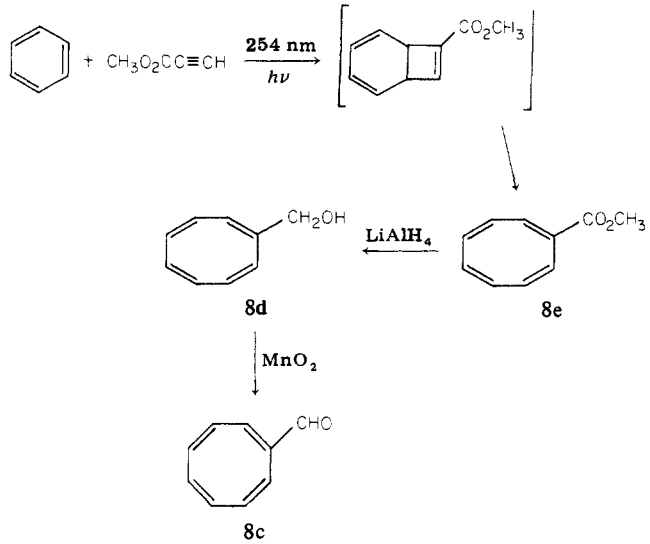
[a] 2,4-Dinitrophenylhydrazone. [b] Uv spectra were determined as 0.5% solutions in 95% EtOH. [c] J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds", Prentice-Hall, Englewood Cliffs, N.J., 1965, Chapter 2.

**Synthesis.** Aldehydes **1c**, **2c**, and **4c–8c** were the key intermediates of the synthetic sequence. The aldehydes were conveniently converted to their corresponding cyanohydrins (**1b**, **2b**, **4b–8b**) and these were subsequently reduced with lithium aluminum hydride in dimethoxyethane to the desired ethanolamines which were isolated as their hydrochloride salts **1a**, **2a**, and **4a–8a**. Aldehydes **1c**, **2c**, and **4c** were commercially available and were converted smoothly to the corresponding ethanolamine hydrochlorides.

Aldehydes **5c**, **6c**, and **7c** were synthesized as outlined in Scheme I. The vinyl bromides **5e**, **6e**, and **7e** were obtained by bromination of, respectively, cyclooctene, cycloocta-1,3-diene, and cycloocta-1,5-diene with pyridinium hydrobromide perbromide followed by elimination of HBr with base. The yield of vinyl bromide obtained varied depending on the base used and the results for a variety of bases are summarized in Table I. Conversion of the vinyl bromides to the corresponding nitriles **5d**, **6d**, and **7d** proceeded smoothly using NaCN–CuCN as described by House.[9] Aldehydes **5c**, **6c**, and **7c** were obtained by reduction of the nitriles using a 3:2 ratio of diisobutylaluminum hydride to nitrile.[10] These aldehydes were converted, through the cyanohydrins, to ethanolamine hydrochlorides **5a**, **6a**, and **7a**.

The substituent on the cycloocta-1,3-diene ring was established to be in the 2 position by analysis of the NMR spectrum of bromide **6e** and the uv spectrum of the 2,4-dinitrophenylhydrazone of aldehyde **6c**. 1-Bromocyclooctene (**5e**) exhibited two multiplets in its NMR spectrum for the allylic methylene protons. Those protons adjacent to the bromine atom were deshielded (δ 3.00–2.43 ppm) compared to those not adjacent to the bromine (δ 2.30–1.83 ppm). 2-Bromocycloocta-1,3-diene (**6e**) showed

Scheme II




a single multiplet in its NMR spectrum for all four allylic methylene protons (δ 2.70–1.87 ppm). 1-Bromocycloocta-1,5-diene (**7e**) exhibited a deshielded multiplet (δ 3.70–2.67 ppm) for the allylic methylene protons adjacent to the bromine with the six other methylene protons giving rise to a multiplet at δ 2.67–1.47 ppm. The ultraviolet absorption maxima of the 2,4-dinitrophenylhydrazone derivatives of aldehydes **5c** and **6c** are shown in Table II. These data are all consistent with substitution in the 2 position in **6e** and **6c**.

1-Formylcyclooctatetraene (**8c**) was prepared as outlined in Scheme II. The cyclooctatetraene ring system was constructed using the photocycloaddition of methyl propiolate to benzene in a modification of a procedure originally described by Bryce-Smith.[11] In their original report, a very small yield of ester **8e** was obtained and an elaborate quartz-wool scrubber for the photochemical immersion well was required because of polymer formation during the photochemical reaction. We found that by using a less intense light source (see Experimental Section) and periodically removing the unreacted starting materials by distillation from ester **8e** and polymeric products, a preparatively useful procedure for the generation of carbomethoxycyclooctatetraene resulted (**8e**). This ester was reduced in nearly quantitative yield with lithium aluminum hydride to give alcohol **8d** which was subsequently oxidized with activated manganese dioxide[12] in good yield to the desired aldehyde **8c**. This aldehyde was converted to the cyanohydrin **8b** with sodium cyanide following the procedure of Corey.[13] Reduction of cyanohydrin **8b** with lithium aluminum hydride in dimethoxyethane produced the ethanolamine which was isolated as its hydrochloride **8a**.

**Pharmacology.** Ethanolamines **1a–8a** were compared with norephedrine (**9**) in their ability to produce a contraction of the normal rat vas deferens. A dose of $3 \times 10^{-4}$ *M* (−)-norepinephrine produced the 100% contraction. The percent of tension produced within 1 min by the test compounds is shown in Figure 1. At a concentration of $3 \times 10^{-4}$ *M* of the test compounds, the order of potency found was **9 > 3 > 1a > 2a > 4a = 5a > 8a > 7a = 6a**. The results are also expressed as the percent of tension measured 5 min after the test compound was added. These results are recorded in Figure 2. The order of potency found was **9 = 2a > 3 > 1a > 4a > 5a > 6a = 7a = 8a**. Since these substances do not produce contraction in the reserpine-pretreated preparations the effects must be indirect.

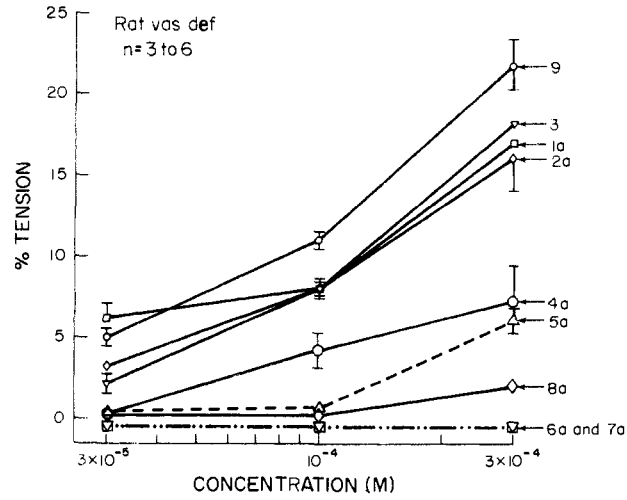



**Figure 1.** Effects of compounds **1a–9** on the normal rat vas deferens. Each concentration was tested in three to six different tissues. The change in tension, within 1 min, after the addition of the drug is expressed as percent of maximum response obtained with (−)-norepinephrine.

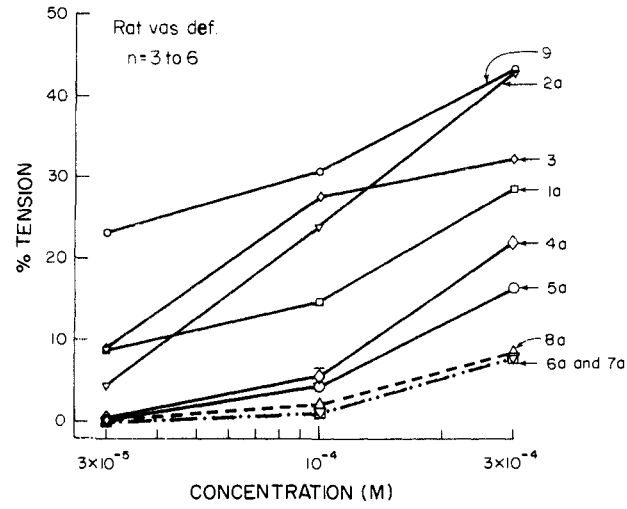
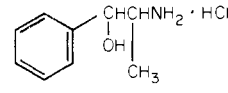



**Figure 2.** Effects of compounds **1a–9** on the normal rat vas deferens. Experiments were the same as in Figure 1 except the change in tension within 5 min after the addition of the drug is expressed as the percent of the maximum response obtained with (−)-norepinephrine.




**9**

In a second set of experiments the ability of compounds **1a–6a, 8a,** and **9** to potentiate the effect of norepinephrine on reserpinized rat vas deferens was studied. A norepinephrine concentration of $3 \times 10^{-4}$ *M* produced the maximum contraction of the tissue; at a concentration of $1 \times 10^{-6}$ *M* it produced a contraction of 20–24%. The percent tension produced by $1 \times 10^{-6}$ *M* norepinephrine in the presence of the indicated test compound is shown in Figure 3. The relative potency of the compounds at a concentration of $3 \times 10^{-5}$ *M* was **9 > 3 = 2a > 4a > 1a > 6a > 5a = 8a**. None of the test compounds (**1a–6a** and **8a**) showed direct α-adrenoceptor activity on the reserpinized rat vas deferens at the concentrations shown in Figure 3.

## Discussion

At the maximum concentrations studied in our experiments ($3 \times 10^{-4}$ *M*) aromatic **3** shows only an indirect

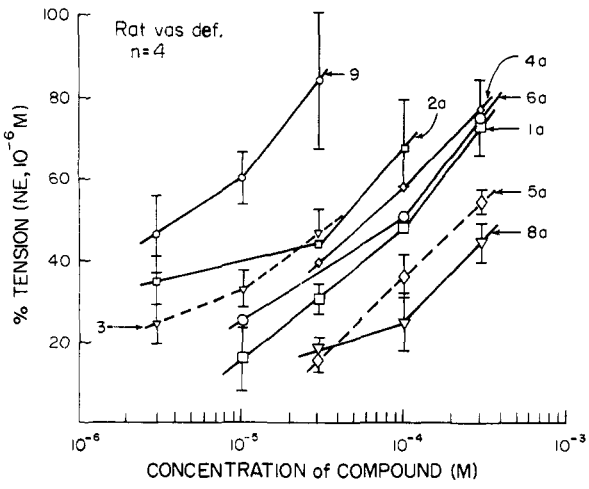



Figure 3. Response of the vas deferens from reserpine-pretreated rats to $1 \times 10^{-6}$ *M* norepinephrine (NE) after prior incubation with the indicated concentrations of test compound. The ordinate records the percent tension of the tissue (the 100% contraction was produced by $3 \times 10^{-4}$ *M* NE). All responses in excess of 22 ± 2% (the percent tension produced by $1 \times 10^{-6}$ *M* NE on the contralateral vas deferens of the same animal) represent potentiation of the response by the test compound.

α-adrenergic effect. It is thus not at all surprising that none of the ethanolamines of this study (**1a–6a** and **8a**) showed direct α-adrenoceptor activity.

From the studies on the normal (nonreserpinized) rat vas deferens, it is not clear if the analogs are acting to cause a release of intraneuronal norepinephrine or to block the uptake of released catecholamines. In the experiment on the reserpinized vas deferens, however, the most logical explanation for the observed potentiation of exogenous norepinephrine would be the blockade of reuptake of the catecholamine since the intraneuronal storage sites were depleted of norepinephrine by the reserpine pretreatment. Within the limits of experimental error, the relative orders of potency are the same between the normal and reserpinized vas deferens experiments. It is likely, therefore, that the major effect of these compounds is a blockade of the amine uptake mechanism.

From the data in Figures 1–3 it is seen that there is no evidence for a π complex between the ethanolamines and the adrenergic amine uptake site of the vas deferens. In fact, the order of potency is nearly the reverse of that to be expected if a π complex were an essential part of interaction at this adrenergic site. It is seen that the more unsaturated analogs (**6a** and **8a**) are the least potent in both normal and reserpinized vas deferens experiments; the more saturated analogs (e.g., **1a** and **4a**) are among the most potent in both experiments.

It is also seen that the six-membered ring analogs rank at the top of the potency list in both experiments in comparison to the eight-membered ring analogs. This may well suggest a steric or ring-size limitation for proper fit at the neuronal uptake site. The fact that the saturated analogs are the more potent would argue that lipophilicity is also very important. It is not possible to make any conclusions regarding the importance of conformational differences among the analogs in terms of observed activity at this time.

The striking and unexpected observations we reported earlier[1] for the activity of these same compounds as substrates for phenylethanolamine *N*-methyltransferase are thus in complete accord with those reported above. The PNMT results are summarized in Table III. If the $K_m$ values are taken as a rough measure of the binding affinity of the ethanolamine derivatives for the active site of the enzyme, it is seen that the order of potency in the eight-membered ring series is **4a > 5a > 6a > 7a > 8a**; namely, the more unsaturated and the more the capability for π-complex formation, the less the binding affinity for the active site of PNMT. The $V_{max}$ of all these nonaromatic analogs of β-phenylethanolamine are similar and all analogs are good substrates for the enzyme. There is thus not only no requirement for π-complex interaction at the active site but no requirement for the ethanolamine to contain an aromatic ring.

Table III. Michaelis-Menten Constants for Nonaromatic Analogs of Phenylethanolamine as PNMT Substrates[a]

| Compd | Kinetic constants[b,c] | |
|---|---|---|
| | $K_m$, μM ± SEM | $V_{max}$ ± SEM[d] |
| 3 | 136 ± 12 | 2.1 ± 0.07 |
| 2a | 57 ± 6.8 | 1.37 ± 0.08 |
| 1a | 40 ± 1 | 0.99 ± 0.11 |
| 8a | 430 ± 45 | 1.73 ± 0.1 |
| 7a | 155 ± 20 | 2.75 ± 0.25 |
| 6a | 128 ± 14 | 2.61 ± 0.19 |
| 5a | 110 ± 8 | 1.92 ± 0.09 |
| 4a | 26 ± 4 | 0.96 ± 0.08 |

[a] PNMT was purified from bovine adrenal medulla (Pel-Freez Biologicals) according to the procedure of R. J. Connett and N. Kirshner, *J. Biol. Chem.*, 245, 329–334 (1970). The purification was carried through the isoelectric precipitation and dialysis steps, which resulted in a sixfold purification of the enzyme from the crude supernatant. [b] PNMT was assayed using the procedure of R. T. Borchardt in R. T. Borchardt and Y. S. Wug, *J. Med. Chem.*, 18, 300–304 (1975). [c] Reciprocal velocities were plotted graphically against reciprocals of the substrate concentrations. The data in the linear region of these plots were used to calculate the $K_m$ and $V_{max}$ using a least-squares method. [d] nmol of product formed/mg of protein/min.

In contrast to the vas deferens data above, there seems to be a less restrictive requirement for ring size at the active site of PNMT since the eight-membered analogs (e.g., **4a**) are as good or better substrates than the six-membered compounds (e.g., **1a**).

Thus we have demonstrated that in these two adrenergic sites, the peripheral neuronal uptake site and the active site of PNMT, there is clearly no requirement for a specific π-complex or less specific charge-transfer interaction between the ring moiety and either adrenergic site.

The implications of these results are under active investigation in these laboratories and these compounds are being evaluated at other adrenergic sites. Additionally, inhibitors of PNMT that do not contain an aromatic ring will be explored.

## Experimental Section

All melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalyses were performed on either an F & M 185A C, H, N analyzer or a Hewlett-Packard 185B C, H, N analyzer and were within 0.4% of theoretical values. Infrared spectra were recorded on either a Beckman IR-10 or IR-33 spectrophotometer. NMR data were recorded on a Varian T-60 spectrometer with $Me_4Si$ as the internal standard. Mass spectra were obtained on a Varian Atlas CH-5 mass spectrometer. Uv determinations were carried out on a Cary 14 spectrophotometer as 0.5% solutions in 95% EtOH. The silica gel used was Brinkman silica gel 60 (70–230 mesh) of activity grade III.

A solution of lithium aluminum hydride ($LiAlH_4$) in dimethoxyethane (DME) was prepared by refluxing a mixture of lump $LiAlH_4$ with DME for 6 hr under $N_2$ and filtering in a drybox for storage in a nitrogen purged, dry bottle fitted with a rubber septum.

**Carbomethoxycyclooctatetraene (8e).** Methyl propiolate (75 ml, 0.882 mol) and 1425 ml of benzene were irradiated in a 1.7-l. cylindrical quartz vessel[11] with a Rayonet RPR 208 pho-

tochemical reactor (The Southern New England Ultraviolet Co., Middletown, Conn. 06457) at 253.7 nm for 20 hr. The yellow solution was distilled (78°), and the clear distillate was reirradiated in a clean vessel as above for 20 cycles. The residue (140 g) was chromatographed in 30-g portions, applied neat, to 300 g of silica gel (4 × 59.5 cm) and eluted with 5% ether–hexanes yielding 53 g (37%) of ester **8e**: bp 50° (0.3 mm) [lit.[11] 89° (0.4 mm)]; $n^{25}$D 1.5914 (lit.[13,14] 1.5938). Anal. ($C_{10}H_{10}O_2$) C, H.

**Cyclooctatetraenylmethyl Alcohol (8d).** Ester **8e** (20 g, 0.124 mol) in 225 ml of $Et_2O$ was added slowly to 4.7 g (0.124 mol) of $LiAlH_4$ in 100 ml of $Et_2O$ under $N_2$. The solution was stirred at 25° for 3 hr, quenched with wet $Na_2SO_4$ followed by 10 ml of 1 *N* HCl, filtered, and dried ($Na_2SO_4$). The solvent was evaporated leaving 16.5 g of yellow oil which gave 16 g (97%) of **8d** after distillation: bp 58–62° (0.3 mm); $n^{25}$D 1.5605 [lit.[15] bp 66–72° (0.5 mm); $n^{25}$D 1.5602]. Anal. ($C_9H_{10}O$) C, H.

**1-Formylcyclooctatetraene (8c).** Alcohol **8d** (4.10 g, 0.03 mol) in 30 ml of $CCl_4$ was added to 20 g of activated $MnO_2$[12] in 170 ml of $CCl_4$. The suspension was stirred vigorously at 25° for 24 hr and filtered and the solvent removed in vacuo leaving 3.75 g of orange oil which was chromatographed on 200 g of silica gel (3.17 × 49.6 cm; 15% $Et_2O$–hexanes) yielding 3.4 g (84%) of aldehyde **8c**: bp 32° (0.05 mm) [lit.[16] 40–45° (0.5 mm)]; $n^{25}$D 1.5718. Anal. ($C_9H_8O$) C, H.

**2-Cyclooctatetraenyl-2-hydroxyacetonitrile (8b).** Aldehyde 8c (6.60 g, 0.05 mol) in 50 ml of $Et_2O$ was added to a solution of NaCN (2.90 g, 0.059 mol) in 20 ml of $H_2O$ at 5°. HCl (concentrated) (4.10 ml, 0.049 mol) was added keeping the temperature between 2 and 5°. The solution was stirred for 3 hr at 5°, the layers were separated, and the aqueous layer was extracted with $Et_2O$ (2 × 50 ml). The combined $Et_2O$ extracts were washed with saturated NaCl solution (2 × 50 ml) and dried ($Na_2SO_4$). Evaporation of the solvent in vacuo gave 7.65 g (96%) of **8b**: ir (neat) 3450 (OH), 2250 $cm^{-1}$ (CN). The cyanohydrin was used directly without further purification.

**2-Cyclooctatetraenyl-2-hydroxyethylamine Hydrochloride (8a).** The crude cyanohydrin **8b** (7.00 g, 0.044 mol) in 20 ml of DME was added slowly to 46 ml (0.035 mol) of a 0.77 *M* $LiAlH_4$–DME solution under $N_2$. The solution was stirred at reflux for 17 hr and cooled, and water (1.4 ml) was added followed by 15% NaOH solution (1.4 ml) and water (4.2 ml). The suspension was filtered and the filtrate dried ($K_2CO_3$). The volume was reduced to 50 ml and $Et_2O$ saturated with HCl (300 ml) was added yielding 4.1 g of brown solid (mp 113–120°) which was recrystallized from MeOH–$Et_2O$ (1:20 v/v) to constant melting point yielding 1.5 g (17%) of amine hydrochloride **8a**: mp 140° dec. Anal. ($C_{10}H_{14}NOCl$) C, H, N.

**1-Bromocyclooctene (5e).** Cyclooctene (15 g, 0.14 mol), pyridinium hydrobromide perbromide (43.7 g, 0.14 mol), and HOAc (100 ml) were stirred for 10 min. The solution was diluted with water (100 ml) and extracted with $CH_2Cl_2$ (4 × 50 ml). The extracts were washed with saturated $NaHCO_3$ (3 × 50 ml) and dried ($Na_2SO_4$) and the solvent was removed in vacuo leaving 35.1 g (95%) of crude 1,2-dibromocyclooctane.

The dibromide (27 g, 0.10 mol) in 40 ml of *t*-BuOH was added to *t*-BuOK (14 g, 0.125 mol) in 50 ml of $Me_2SO$–30 ml of *t*-BuOH at 5–15° with stirring under $N_2$. The mixture was stirred at 25° for 18 hr, diluted with water (200 ml), and extracted with hexanes (6 × 50 ml). The extracts were washed with water (3 × 100 ml) and dried ($MgSO_4$) and the solvent was removed in vacuo leaving 19 g of oil which was distilled to yield 8.10 g (43%) of bromide **5e**: bp 30–32° (0.15 mm); $n^{27}$D 1.5168 [lit.[18] 97–98° (23 mm); lit.[19] $n^{20}$D 1.5182]; mass spectrum (70 eV) *m/e* (rel intensity) 191 ($M^+$ + 2, 0.9), 189 ($M^+$, 1).

**1-Cyanocyclooctene (5d).** Bromide **5e** (10 g, 0.053 mol) in 30 ml of DMF was added slowly to NaCN (5.2 g, 0.106 mol) and $Cu_2CN_2$ (9.5 g, 0.106 mol) in 150 ml of warm DMF under $N_2$. The mixture was stirred at reflux for 5 hr, poured hot into 400 ml of a 25% NaCN solution, and extracted with benzene (3 × 100 ml). The combined extracts were washed with a 25% NaCN solution (3 × 100 ml) and dried ($Na_2SO_4$) and the solvent was removed in vacuo leaving 7.75 g of clear oil which was distilled yielding 6.65 g (93%) of cyanide **5d**. The distillate was applied to 600 g of silica gel (4.8 × 50.4 cm; 20% $Et_2O$–hexanes) yielding 4.2 g (59%) of **5d**: bp 42° (0.10 mm); $n^{28}$D 1.5102. Anal. ($C_9H_{13}N$) C, H, N.

**1-Formylcyclooctene (5c).** *i*-$Bu_2AlH_2$ (12.5 g, 0.09 mol) in 80 ml of hexanes was added with stirring under $N_2$ in an ice bath to compound **5d** (7.95 g, 0.06 mol). After stirring for 14 hr at 45°, MeOH (8.5 g) was added followed by water (4.85 g) and MeOH (15 ml). The suspension was filtered, the filtrate dried ($MgSO_4$), and the solvent removed in vacuo. The residue was treated with semicarbazone reagent (0.09 mol) yielding 8.0 g (70%) of semicarbazone (mp 213–217° dec). The crude semicarbazone was heated with HOAc (50 ml) and 50% pyruvic acid (50 ml) on a steam bath for 45 min. The mixture was diluted with water (500 ml) and extracted with hexanes (5 × 50 ml). The combined extracts were washed with water (2 × 100 ml) and saturated $NaHCO_3$ (50 ml) and dried ($CaCl_2$). After evaporation of the solvent in vacuo, the oily residue was distilled yielding 3.0 g (37%) of aldehyde **5c**: bp 35° (0.22 mm); $n^{27}$D 1.5022. A portion of the semicarbazone derivative was recrystallized from MeOH to a constant melting point of 219–220°. Anal. ($C_{10}H_{17}N_3O$) C, H, N.

**2-Cyclooctenyl-2-hydroxyacetonitrile (5b).** The procedure was the same as described for cyanohydrin **8b**. Aldehyde **5c** (3.80 g, 0.0275 mol) in 15 ml of $Et_2O$ was added to NaCN (2.9 g, 0.059 mol) in 10 ml of water yielding 4.40 g (97%) of cyanohydrin **5b** upon work-up: ir (neat) 3450 (OH), 2250 $cm^{-1}$ (CN). The cyanohydrin **5b** was used without further purification in the next step.

**2-Cyclooctenyl-2-hydroxyethylamine Hydrochloride (5a).** The procedure was the same as described for amine hydrochloride **8a**. The cyanohydrin **5b** (4.35 g, 0.026 mol) in 10 ml of DME was added to 28 ml (0.0215 mol) of a 0.77 *M* solution of $LiAlH_4$–DME yielding 2.25 g (42%) of white solid (mp 140–142°). Recrystallization from hot MeOH, to which $Et_2O$ was added until the cloud point was reached, yielded 1.45 g (27%) of **5a**: mp 176–177°. Anal. ($C_{10}H_{20}NOCl$) C, H, N.

**2-Bromocycloocta-1,3-diene (6e).** The dibromide was prepared as described in the preparation of **5e**. Pyridinium hydrobromide perbromide (44.4 g, 0.139 mol) was added to 1,3-cyclooctadiene (15.05 g, 0.139 mol) in HOAc (100 ml) yielding 31.95 g (86%) of crude 3,4-dibromocyclooctene.

The crude dibromide (31.95 g, 0.119 mol) in *i*-PrOH (30 ml) was added to a warm solution of KOH–*i*-PrOH[20] (20.2 g, 0.306 mol, 175 ml) and stirred at reflux for 23 hr. After cooling, water (500 ml) was added and the aqueous phase extracted with $Et_2O$ (4 × 100 ml). The combined $Et_2O$ extracts were washed with water (2 × 200 ml) and dried ($Na_2SO_4$) and the solvent was removed in vacuo giving 17.45 g of oil which was distilled yielding 11.75 g (53%) of **6c**: bp 38° (0.10 mm); $n^{25}$D 1.5235; mass spectrum (70 eV) *m/e* (rel intensity) 189 ($M^+$ + 2, 0.9), 187 ($M^+$, 1).

**2-Cyanocycloocta-1,3-diene (6d).** The procedure was the same as described for compound **5d**. The bromide **6e** (21.05 g, 0.113 mol) in DMF (50 ml) was added to a hot solution of NaCN (11.05 g, 0.23 mol) and $Cu_2CN_2$ (20.2 g, 0.23 mol) in DMF (100 ml). Upon work-up 11.85 g of oil was obtained which was chromatographed on silica gel (50.4 × 4.8 cm; 20% $Et_2O$–hexanes) and distilled yielding 7.45 g (50%) of cyanide **6d**: bp 40–44° (0.05 mm); $n^{28}$D 1.5118; peak matching from the mass spectrum; calcd mass, 133.08909; found, 133.08859.

**2-Formylcycloocta-1,3-diene (6c).** The procedure was the same as described for aldehyde **5c**. *i*-$Bu_2AlH_2$ (9.85 g, 0.069 mol) in hexane (63 ml) was added to cyanide **6d** (6.15 g, 0.046 mol) yielding 7.35 g (82%) of semicarbazone (mp 206–208°) upon work-up. Hydrolysis of the semicarbazone yielded 2.05 g (33%) of aldehyde **6c** after distillation: bp 34° (0.3 mm); $n^{27}$D 1.5346. A portion of the semicarbazone was recrystallized from MeOH to a constant melting point of 216–217°. Anal. ($C_{10}H_{15}N_3O$) C, H, N.

**2-(Cycloocta-1,3-dien-2-yl)-2-hydroxyacetonitrile (6b).** The procedure was the same as described for compound **8b**. The aldehyde **6c** (1.7 g, 0.013 mol) in $Et_2O$ (30 ml) was added to NaCN (1.3 g, 0.027 mol) in water (10 ml) giving 1.85 g (91%) of cyanohydrin **6b**: ir (neat) 3450 (OH), 2250 $cm^{-1}$ (CN). The cyanohydrin **6b** was used without further purification in the next procedure.

**2-(Cycloocta-1,3-dien-2-yl)-2-hydroxyethylamine Hydrochloride (6a).** The procedure used was the same as described for amine hydrochloride **8a**. Cyanohydrin **6b** (1.65 g, 0.01 mol) in DME (10 ml) was added to 11 ml (0.0084 mol) of a $LiAlH_4$–

DME solution (0.77 *M*) giving 0.75 g (36%) of tan solid (mp 140–141°) which was recrystallized from MeOH–$Et_2O$ (1:20 v/v) yielding 0.50 g (24%) of amine hydrochloride **6a**: mp 149–150° dec. Anal. ($C_{10}H_{18}NOCl$) C, H, N.

**1-Bromocycloocta-1,5-diene (7e).** The dibromide was prepared as described under compound **5e**. Pyridinium hydrobromide perbromide (63.95 g, 0.20 mol) was added to 1,5-cyclooctadiene (21.63 g, 0.20 mol) in HOAc (100 ml) yielding 51.45 g (96%) of crude 5,6-dibromocyclooctene. The dibromide was used without further purification.

1,5-Diazabicyclo[4.3.0]undec-5-ene[21] (10.8 g, 0.07 mol) in benzene (50 ml) was added to the dibromide (18.45 g, 0.07 mol) in benzene (50 ml) and refluxed with stirring under $N_2$ for 20 hr. After cooling the mixture was poured into 1 *N* $H_2SO_4$–ice (160 ml) with stirring and extracted with $Et_2O$ (3 × 175 ml), and the combined extracts were dried ($Na_2SO_4$). Evaporation of the solvent in vacuo gave 15.20 g of oil which was distilled to give 4.00 g (31%) of **7e**: bp 43° (0.5 mm); mass spectrum (70 eV) *m/e* (rel intensity) 189 ($M^+$ + 2, 3), 187 ($M^+$, 3).

**1-Cyanocycloocta-1,5-diene (7d).** The procedure used was the same as described for compound **5d**. The bromide **7e** (11.05 g, 0.059 mol) in DMF (40 ml) was added to NaCN (5.80 g, 0.12 mol) and $Cu_2CN_2$ (10.6 g, 0.12 mol) in hot DMF (90 ml) giving 7.55 g of oil which was distilled to yield 3.65 g (47%) of **7d**: bp 42–46° (0.10 mm); $n^{27}D$ 1.5085; peak matching in mass spectrum; calcd mass, 133.08909; found, 133.08915.

**1-Formylcycloocta-1,5-diene (7c).** The procedure used was the same as used for aldehyde **5c**. *i*-$Bu_2AlH_2$ (6.38 g, 0.045 mol) in hexane (42 ml) was added to **7d** (4.05 g, 0.031 mol) giving 2.75 g (49%) of crude semicarbazone which was hydrolyzed to give 1.05 g (25%) of aldehyde **7c** after distillation: bp 38–39° (0.3 mm); $n^{25}D$ 1.5232. A portion of the semicarbazone was recrystallized from MeOH to a constant melting point of 208–209°. Anal. ($C_{10}H_{15}N_3O$) C, H, N.

**2-(Cycloocta-1,5-dienyl)-2-hydroxyacetonitrile (7b).** The procedure used was the same as described for cyanohydrin **8b**. Aldehyde **7c** (1.00 g, 0.007 mol) in $Et_2O$ (20 ml) was added to NaCN (0.4 g, 0.008 mol) in water (10 ml) giving 1.10 g of oil which was a 1:1 mixture of aldehyde **7c** and cyanohydrin **7b**. The mixture was used without further purification in the next step.

**2-(Cycloocta-1,5-dienyl)-2-hydroxyethylamine Hydrochloride (7a).** The procedure used was the same as described for amine hydrochloride **8a**. The **7b–7c** mixture above (0.8 g) in DME (10 ml) was added to 5.1 ml (0.004 mol) of a $LiAlH_4$–DME solution (0.77 *M*) which gave 50 mg (6%) of amine hydrochloride **7a** upon work-up: mp 133–136° dec. Anal. ($C_{10}H_{18}NOCl$) C, H, N.

**2-Cyclooctyl-2-hydroxyacetonitrile (4b).** The procedure used was the same as described for cyanohydrin **8b**. Cyclooctanecarboxaldehyde (Aldrich, 14.0 g, 0.10 mol) in $Et_2O$ (100 ml) was added to NaCN (5.80 g, 0.118 mol) yielding 16.90 g (100%) of **6b**: ir (neat) 3460 (OH), 2250 $cm^{-1}$ (CN). The cyanohydrin was used without further purification in the next step.

**2-Cyclooctyl-2-hydroxyethylamine Hydrochloride (4a).** The procedure used was the same as described for amine hydrochloride **8a**. Cyanohydrin **4b** (11.80 g, 0.07 mol) in DME (20 ml) was added to 74 ml (0.057 mol) of a $LiAlH_4$–DME solution (0.77 *M*) giving 5.90 g (49%) of amine hydrochloride **4a**: mp 228–229°. Anal. ($C_{10}H_{22}NOCl$) C, H, N.

**2-(Cyclohexen-4-yl)-2-hydroxyacetonitrile (2b).** The procedure used was the same as described for cyanohydrin **8b**. 4-Formylcyclohexene (Aldrich, 11 g, 0.10 mol) in $Et_2O$ (100 ml) was added to NaCN (5.80 g, 0.12 mol) in water (40 ml) yielding 13.60 g of cyanohydrin **2b**: ir (neat) 3450 (OH), 2250 $cm^{-1}$ (CN). The cyanohydrin was used without further purification in the next step.

**2-(Cyclohexen-4-yl)-2-hydroxyethylamine Hydrochloride (2a).** The procedure used was the same as described for amine **8a**. Cyanohydrin **2b** (12 g, 0.09 mol) in DME (30 ml) was added to 91 ml (0.07 mol) of a $LiAlH_4$–DME solution (0.77 *M*) yielding 5.55 g (36%) of white solid (mp 130–135°) which was recrystallized from MeOH–$Et_2O$ (1:20 v/v) giving 4.0 g (26%) of amine hydrochloride **2a**: mp 140–142°. Anal. ($C_8H_{16}NOCl$) C, H, N.

**2-Cyclohexyl-2-hydroxyacetonitrile (1b).** The procedure used was the same as described for cyanohydrin **8b**. 1-Formylcyclohexane (Aldrich, 5.60 g, 0.05 mol) in $Et_2O$ (55 ml) was added to NaCN (2.90 g, 0.059 mol) in water (20 ml) yielding 6.70 g (97%) of **1b**: ir (neat) 3450 (OH), 2250 $cm^{-1}$ (CN). The cyanohydrin was used without further purification in the next step.

**2-Cyclohexyl-2-hydroxyethylamine Hydrochloride (1a).** The procedure used was the same as described for amine hydrochloride **8a**. Cyanohydrin **1b** (6.0 g, 0.043 mol) in DME (20 ml) was added to 45 ml (0.035 mol) of a $LiAlH_4$–DME solution (0.77 *M*) yielding 1.95 g (28%) of amine hydrochloride **1a**, a portion of which was recrystallized from MeOH–$Et_2O$ (1:20 v/v): mp 204–206°. Anal. ($C_8H_{18}NOCl$) C, H, N.

**Pharmacological Testing.** Male albino Sprague–Dawley derived rats of weight 200–710 g obtained from Harlan or Lab Supply, Cumberland, Ind., were used in this study. The rats received 5 mg/kg of reserpine ip 18–22 hr prior to the experiment.

The animals were decapitated and the vas deferens was quickly removed, cleaned of blood vessels and fatty tissue, and mounted in a 10-ml jacketed tissue bath containing modified Krebs solution of the following composition as millimoles per liter in double distilled water: NaCl, 118; KCl, 4.7; $MgCl_2 \cdot 6H_2O$, 0.54; $CaCl_2 \cdot 2H_2O$, 2.5; $Na_2HPO_4$, 1.0; $NaHCO_3$, 25; glucose, 11. Ethylenediaminetetraacetic acid (EDTA) (10 mg/l.) was added to retard the spontaneous oxidation of (–)-norepinephrine. This concentration of EDTA chelates a negligible amount of calcium in the medium. A mixture of 95% $O_2$ and 5% $CO_2$ gas was bubbled through the solution, and the temperature was kept at 37 ± 0.5°.

Responses of vas deferens to drugs were recorded isometrically under 0.25-g tension via a Grass force displacement transducer Model FT-03-C on a Grass Model 7C polygraph. The tissues were left to equilibrate for 1 hr with frequent washing with new aliquots of Krebs solution. The response of the vas deferens from one side was recorded to a dose of 1 × $10^{-6}$ *M* (–)-norepinephrine which usually produced contraction between 20 and 30% of the maximal. This experiment was performed to check day to day variability in control values. The tissue was washed until the response returned to baseline and a dose of 3 × $10^{-4}$ *M* (–)-norepinephrine was given to produce 100% contraction. The vas deferens from the contralateral side was incubated with a given concentration of the compound under test for 15 min, and at the end of this period the standard dose of 1 × $10^{-6}$ *M* (–)-norepinephrine was given to test the response of the tissue in the presence of the compound. Subsequently, the tissue was washed several times and the response to (–)-norepinephrine, 3 × $10^{-4}$ *M*, was obtained. The change in response to a 1 × $10^{-6}$ *M* dose of (–)-norepinephrine was calculated as percent in terms of maximum response obtained with the high dose of (–)-norepinephrine. At least three different concentrations of each compound were used.

In another series of experiments, the indirect activity of the compounds was tested. The normal (nonreserpinized) rat vas deferens was utilized. They were set up as above and left to equilibrate before the start of the experiment. The activity of the compounds was tested at three different concentrations for up to 5 min each time. The tissue was then washed and norephedrine in the same concentration as the test compound was added to serve as internal control. After this time the norephedrine was washed away, and a dose of 3 × $10^{-4}$ *M* (–)-norepinephrine was given to attain a response which served as the 100% effect. The effects of the compounds under test as well as those of the internal control were calculated as percent changes in tension of the maximum response in the same tissue.

Drug solutions were prepared fresh on the day of the experiment in saline containing 0.05% of sodium metabisulfite to prevent autooxidation of catecholamines.

(–)-Norepinephrine (Regis Co.) was used as the free base and dissolved with the aid of a few drops of 0.1 *N* HCl.

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# Relationship between Analgetic $ED_{50}$ Dose and Time-Course Brain Levels of *N*-Alkylnormeperidine Homologues[1]

Dennis L. Larson and Philip S. Portoghese*

*Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota 55455.*
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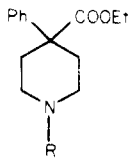
The brain levels of meperidine and three *N*-alkyl homologues were determined at equal analgetic iv doses in mice. The relative levels of the four compounds in brain were found to be closely proportional to their $ED_{50}$ doses even though the compounds exhibit a wide range in partition coefficient and metabolic N-dealkylation. While lipid solubility and metabolism are undoubtedly important factors in the overall time-course brain levels, it appears that during the period of analgetic measurement (5–60 min after injection) these factors do not profoundly affect the relative brain levels because peak uptake occurs within the first 5 min after administration of the homologues. As a consequence, the observed $ED_{50}$ potencies appear to provide a fair approximation of the relative receptor affinities of the four homologues. N-Dealkylation was observed as a major metabolic transformation by mouse liver in vivo for all four compounds, and the extent of this N-dealkylation was found to directly correspond to the rates of N-dealkylation by mouse liver homogenate seen in an earlier study.

Homologous series of analgetics that differ only in the N-substituent often show variation in the $ED_{50}$ potency.[2] Although this simple structural modification usually does not lead to dramatic potency changes in the 4-phenylpiperidine class, the question concerning the origin of this potency variation is as yet unresolved. Thus, variation in $ED_{50}$ potency may be due to receptor-related events, differential access to the biophase, or some combination of these.

For example, a homologous series of alkylnorketobemidones shows a good correlation between relative ability to bind mouse brain homogenate in vitro and their in vivo hot-plate analgetic potencies.[3] This observation suggests that within this series factors such as metabolism and distribution do not appear to have a profound effect on relative potency. A similar result was found in the same type of study on a series of *N*-alkyl derivatives of benzazocine.[4] By contrast, we have previously reported[5] a correlation between the analgetic $ED_{50}$ doses of *N*-alkyl derivatives of normeperidine (1, R = H) in mice and their in vitro rates of N-dealkylation. The homologues which exhibited a greater tendency toward N-dealkylation also had higher $ED_{50}$ values. The high correlation suggested that the relative rates of N-dealkylation in vitro are similar to those in vivo and that the variation in $ED_{50}$ potency with chain length is related primarily to differences in availability to the biophase as a result of metabolism. Other studies[6,7] involving intraventricular administration of analgetics tend to implicate liposolubility as an important parameter contributing to relative potency based on standard modes of administration.

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In an effort to determine if the iv $ED_{50}$ potencies of homologous *N*-alkylnormeperidines in mice parallel their brain levels, we have examined the time-course brain concentrations of four members (1, R = Me, *n*-Pr, *n*-Bu, *n*-hexyl) of this series. The results of the present study indicate that the observed potencies represent an approximation of their relative affinities for analgetic receptors.