

members of sets of congeneric inhibitors bound to the enzyme. These studies, which are now possible, will firm up our QSAR-derived conclusions and enable us to more confidently refine QSAR techniques. Such a project is now

under way between our laboratory and that of Kraut and Matthews in La Jolla employing the triazines used to develop the QSAR in this report for dihydrofolate reductase.

Structure-Activity Relationships of the Cycloalkyl Ring of Phencyclidine

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In order to investigate the structural requirements for a cycloalkyl moiety in the potent hallucinogen 1-(1-phenylcyclohexyl)piperidine (PCP, 1), a series of structural analogues was synthesized in which the size of the cycloalkyl ring was varied from three carbons to eight carbons. Biological activities of these compounds were assessed in an in vitro assay (phencyclidine binding assay) and an in vivo assay (discriminative stimulus assay). As the cycloalkyl ring size decreased from that of cyclohexane (PCP), PCP-like activity declined in both assays, but as the cycloalkyl ring size became larger than cyclohexane, a sharp decline in PCP-like activity was observed in the in vivo assay, while activity in the in vitro assay was only slightly less than that of PCP. 1-(1-Phenylcyclooctyl)piperidine (8) had potent competitive binding properties in the in vitro binding assay but produced no observable PCP-like effects in the in vivo assay. The importance of the cycloalkyl ring in the structure of PCP was demonstrated by testing benzylpiperidine (2), which had almost no measurable activity in either assay.

Phencyclidine (PCP, 1) is an easily synthesized and thus readily available drug that has become a substance of major abuse, particularly among teenagers. Agitated, hostile, and aggressive behavior, depressive states, a toxic psychosis, and a number of deaths, including suicides and murders, have been associated with PCP abuse.² PCP (Sernyl) was introduced more than 15 years ago as an anesthetic medication in man, but the high incidence of undesirable side-effects during recovery from anesthesia has precluded its further use in man.³ In spite of PCP's many negative aspects, the euphorogenic properties of PCP have made the drug popular among recreational users.

PCP appears to represent a unique class of drugs whose spectrum of action is readily distinguishable from that of other classes of psychoactive drugs, including narcotics, LSD-like hallucinogens, amphetamine-like stimulants, barbiturate-like depressants, and cholinergic agonists.⁴ Although the pharmacology of PCP has been extensively studied, little is known about the mechanism of action of PCP at the molecular level. In order to gain some understanding of the mechanism of action of PCP, we have undertaken studies to explore the structural requirements for PCP-like activity. The first of these studies is reported in this paper.

An examination of the PCP molecule reveals a semirigid structure in which the interatomic distance between the benzene and piperidine rings is governed by the internal bond angles of the cyclohexane ring. The flexibility of the cyclohexane ring allows these bond angles to conform closely to the theoretical 109.5° bond angles found for normal sp³ hybrid bonding. This relationship was confirmed by Argos et al.⁵ in a study of the molecular structure of PCP·HCl by X-ray crystallography. They found the angle θ (see Table I) to be 109.0°. Also, the distance between the bonding carbon (C7) of the cyclohexyl group and

the nitrogen atom (N13) of the piperidine group was found to be 1.550 Å, while the distance between C7 and the bonding carbon of the phenyl group (C1) was 1.543 Å. Since the value for θ and the distances between C7-Cl and C7-N13 have been experimentally measured, the distance (a) between the nitrogen atom of the piperidine ring and the Cl atom of the phenyl ring can be calculated by utilizing a simple trigonometric relationship ($a^2 = b^2 + c^2 - 2bc \cos \theta$, where b and c are the lengths of the adjacent sides of the angle θ). The distance a was calculated to be 2.518 Å.

PCP has been shown to exhibit anticholinergic activity.⁶ In the case of acetylcholine, the distance that separates the areas of minimum potential between the negatively charged ester oxygen and the positively charged trimethylammonium group has been recognized as a critical parameter in determining cholinergic activity.^{7,8} Since the PCP·HCl molecule also can be visualized as having an area of localized positive charge (the nitrogen atom of the piperidine ring) at a fixed distance (2.518 Å) from an area of negative charge (the delocalized electron cloud of the benzene ring),⁸ it has been suggested that this distance might be a critical parameter in determining PCP-like activity.^{8,9} In order to test whether the distance between the benzene and piperidine ring is critical for PCP-like activity, a series of compounds was prepared in which the angle θ , and consequently the distance a , was systematically altered while leaving the composition of the benzene and piperidine rings unaltered. Assuming that the distances between C7-N13 and C7-Cl of PCP are independent of bond angles and remain constant, the distance a should be directly dependent upon the value of θ . For saturated cycloalkyl ring systems of six carbons or less, the bond angles are dependent upon the ring size. By altering the size of the cycloalkyl ring in PCP, the value for θ and, consequently, the distance between the benzene and piperidine ring can be altered. For rings larger than six

(1) Riker Laboratories, Inc., St. Paul, MN 55101.

(2) R. C. Peterson and R. C. Stillman, *NIDA Res. Monogr.*, no. 21, 1-17 (1978).

(3) E. Domino, *Int. Rev. Neurobiol.*, 6, 303 (1964).

(4) D. R. Jasinski, H. E. Shannon, E. J. Cone, D. B. Vaupel, M. E. Risner, R. L. McQuinn, T.-P. Su, and W. B. Pickworth, in "PCP (Phencyclidine): Historical and Current Perspectives", E. F. Domino, Ed., NNP Books, Ann Arbor, MI, pp 331-400.

(5) P. Argos, R. E. Barr, and A. H. Weber, *Acta Crystallogr., Sect. B*, 26, 53 (1970).

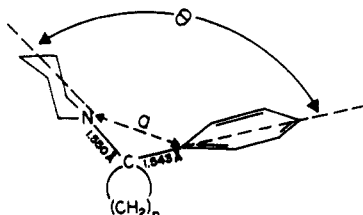
(6) S. Maayani, H. Weinstein, N. Ben-Zvi, S. Cohen, and M. Sokolovsky, *Biochem. Pharmacol.*, 23, 1263 (1974).

(7) J. B. Robinson, B. Belleau, and B. Cox, *J. Med. Chem.*, 12, 848 (1969).

(8) S. Maayani, H. Weinstein, S. Cohen, and M. Sokolovsky, *Proc. Natl. Acad. Sci. U.S.A.*, 70, 3103 (1973).

(9) H. Weinstein, S. Maayani, S. Srebnik, S. Cohen, and M. Sokolovsky, *Mol. Pharmacol.*, 9, 820 (1973).

Table I. Physical Properties of the Hydrochlorides of Some Cycloalkyl-Substituted PCP Analogues



no.	n	yield, ^a %	θ , ^b deg	a, Å	mp, °C	recrystn solvent	formula ^c
2	0	43			184-186	CH ₃ CN ether	C ₁₂ H ₁₈ ClN
3	2	21	116	2.623	195-197	CHCl ₃ ether	C ₁₄ H ₂₀ ClN
4	3	28	111	2.549	243-245	CH ₃ CN	C ₁₅ H ₂₂ ClN
5	4	22	109.5	2.526	239-240	CH ₃ CN	C ₁₆ H ₂₄ ClN
1	5	63	109	2.518	243-244	CH ₃ CN	C ₁₇ H ₂₆ ClN
7	6	53	109	2.518	220-222	CH ₃ CN	C ₁₈ H ₂₈ ClN
8	7	19	109	2.518	182-185	2-propanol	C ₁₉ H ₃₀ ClN

^a Yields are for the last step. ^b The angle θ for compounds where $n = 6$ or 7 was assumed to be equal to that of phenylcyclidine. For compounds where $n = 2, 3$, or 4 , the angle θ was obtained from ref 10. ^c All compounds gave satisfactory analysis for C, H, and N.

carbons, the value for θ will remain essentially the same (109.0°), since their flexibility allows them to achieve the preferred bonding angles for normal sp^3 bonding.

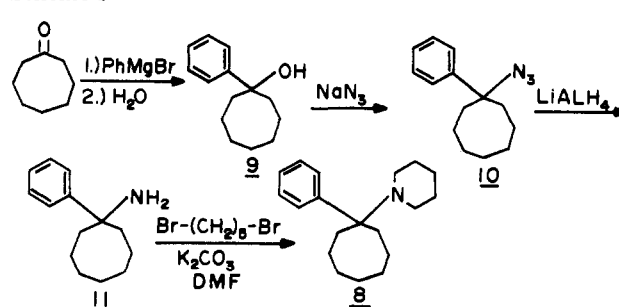
A series of PCP analogues was synthesized in which the size of the cycloalkyl ring was varied from three to eight carbons. The theoretical values for the distance a for these compounds are presented in Table I. The values used for the angle θ are those reported for unsubstituted saturated cycloalkyl ring systems.¹⁰ In addition to the cycloalkyl analogues, compound 2 was prepared to test the necessity of having a cyclic alkyl moiety in the structure of PCP-like compounds.

Chemistry. Compounds 1 and 5 were synthesized according to the procedures outlined by Kalir et al.¹¹ Compounds 4 and 7 were prepared as described by Kalir et al.¹²

The method used to synthesize 3 involved the production of 1-phenylcyclopropanecarbonyl azide and its subsequent rearrangement and reduction to 1-phenylcyclopropylamine, followed by condensation with 1,5-dibromopentane to form the piperidine ring.¹³ The synthesis of 8 involved a two-step reaction to produce 1-phenylcyclooctyl azide (10) and reduction of the azide to 1-phenylcyclooctylamine (11), followed by condensation with 1,5-dibromopentane (see Scheme I). Overall yields were generally low, but purity was high. Compound 2 was made in good yield by refluxing benzylamine (6) in the presence of 1,5-dibromopentane and potassium carbonate in dimethylformamide. The physical properties of the cycloalkyl homologues of PCP and 2 are listed in Table I.

Biological Assay. The biological potency of each of the PCP analogues, relative to PCP, was measured by both an in vitro and an in vivo assay for PCP-like activity. The in vivo assay measures the potency of an analogue, relative to PCP, in producing correct responding in a two-choice, discrete-trial avoidance task by rats trained to discriminate between PCP and saline. Selective responding on the PCP lever is taken to indicate that the analogue is PCP-like or

Scheme I



that its effects generalize to those of PCP. This assay is based upon the previous findings that PCP produces discriminative stimuli in the rat and that the stimuli produced by several PCP structural analogues are generalized to those produced by PCP.¹⁴⁻¹⁶ The in vitro assay measures the displacement by the PCP analogues of [³H]PCP specifically bound to rat brain homogenates using the procedure described by Zukin and Zukin.¹⁷

Results and Discussion

The cycloalkyl homologues of PCP (Table I) were synthesized by systematically altering the size of the cycloalkyl ring in increments of a single methylene unit while maintaining a constant molecular composition for the phenyl and piperidine rings. The biological activity of each compound was measured in both an in vitro and in vivo assay. Relative potencies were determined for each compound by comparing its activity in a particular assay to that of 1 (PCP), which produced maximal activity in both assays. As the cycloalkyl ring size decreased from that of cyclohexane (compounds 3-5), a parallel reduction of relative potency in both assays was observed (see Table II), results consistent with those reported by Kalir¹⁸ for compounds 4 and 5. Although the reduction in ring size and the concomitant increase of a correlate with the ob-

(10) C. A. Coulson and W. Moffitt, *Philos. Mag.*, **40**, 1 (1949).

(11) A. Kalir, H. Edery, Z. Pelah, D. Balderman, and G. Porath, *J. Med. Chem.*, **12**, 473 (1969).

(12) A. Kalir, S. Sadeh, H. Karoly, E. Shirin, D. Balderman, H. Edery, and G. Porath, *Isr. J. Chem.*, **13**, 125 (1975).

(13) C. Kaiser, B. M. Lester, C. L. Zirkle, A. Burger, C. S. Davis, T. J. Delia, and L. Zirngibl, *J. Med. Chem.*, **5**, 1243 (1962).

(14) T. U. C. Jarbe, J. O. Johansson, and B. G. Henriksson, *Psychopharmacologia*, **43**, 33 (1975).

(15) D. A. Overton, *Arch. Int. Pharmacodyn. Ther.*, **215**, 180 (1975).

(16) A. D. Poling, F. J. White, and J. B. Appel, *Neuropharmacology*, **18**, 459 (1979).

(17) S. R. Zukin and R. S. Zukin, *Proc. Natl. Acad. Sci. U.S.A.*, **76**, 5372 (1979).

(18) A. Kalir, *Psychopharm. Bull.*, **16**, 54 (1980).

Table II. Relative Potencies of PCP and Analogues in the [³H]PCP Binding Assay and the Rat Discriminative Stimulus Test (DS)

no.	rel potency	
	[³ H]PCP binding assay ^a	rat DS ^b
2	0.02	IA ^{c,d}
3	0.07	IA ^{c,e}
4	0.08	0.19 (±0.07)
5	0.12	0.37 (±0.13)
1	1.0	1.0
7	0.23	0.06 (±0.05)
8	0.72	IA ^{c,f}

^a In the binding assay, relative potencies were obtained from the IC₅₀ values compared with PCP. The IC₅₀ of PCP was 270 nM. The SD for each sample was less than 4%. ^b The relative potency for each analogue is expressed as the milligrams of PCP equivalent to 1.0 mg of the indicated analogue. ^c Did not generalize to PCP. ^d Produced CNS depression at 56 mg/kg. ^e No activity seen at doses < 56 mg/kg. ^f Tonic seizures were observed at 56 mg/kg.

served decrease in relative potency, it is doubtful that this is the only factor operating in the diminution of PCP-like activity. The change in *a* is calculated to be only 0.008 Å in going from 1 to 5, whereas the relative potency of 5 was only approximately one-eighth that of 1 in the in vitro assay and about one-third of 1 in the in vivo assay. Compound 2 also was tested but showed almost no measurable activity in either assay.

As the cycloalkyl ring of PCP analogues becomes larger than the cyclohexane ring of PCP, the distance between the benzene and piperidine rings is expected to remain approximately the same. Thus, 7 and 8 should differ from PCP only in the bulkiness of the cycloalkyl ring. Such similarity in structure and molecular composition would be expected to yield compounds with similar biological activities. The finding that the relative potencies of 7 and 8 did not markedly differ from 1 as measured by the in vitro binding assay was not unexpected, but when 7 and 8 were assayed for in vivo PCP-like activity, they were found to have almost no measurable activity. Changes in the preferred conformations of the PCP derivatives were considered as a possible explanation of the lack of activity of compounds 7 and 8. PCP has been shown to adopt a conformation with the phenyl group in the axial position and the piperidine ring in an equatorial position.¹⁹ Other PCP derivatives which could adopt a similar conformation were reported to be more active than the corresponding cis-trans isomer. However, the cycloalkyl rings of compounds 7 and 8 are sufficiently flexible to exist in similar conformations to that of PCP, and it seems unlikely that this accounts for their lack of activity. It would appear, then, that the molecular volume or shape of the cycloalkyl ring in PCP-like compounds is equally as important as the distance between the phenyl and piperidine rings in determining in vivo activity.

It seems apparent that even very minor perturbations of the cyclohexane ring are not well tolerated in retaining PCP-like activity. It has been suggested that the cyclohexane ring of PCP contributes to the biological activity of this drug by maintaining the proper structural rigidity of the other two rings and by contributing to hydrophobic binding at the receptor site.²⁰ The latter hypothesis is

consistent with our findings that 7 and 8 displace [³H]PCP in vitro, but is inconsistent with our findings that 8 has virtually no measurable PCP-like activity in vivo. The fact that 7 and 8 bind well at the PCP specific binding site in vitro and yet produce very little measurable activity in vivo suggested the possibility that these two compounds may have partial agonist and/or antagonist properties. However, coadministration of 7 or 8 with 1 did not produce antagonistic effects in the rat discriminative stimulus assay. Another possible explanation for the observed disparity between the binding assay and the discriminative stimulus assay is that there may be more than one binding site for PCP in the brain homogenate preparation. Thus, 7 and 8 may have high affinity for one of these binding sites but little affinity for the site that is most correlated with the easily observable effects of PCP-like drugs. Some support for such a possibility is offered by our observation that 7 and 8 produce a marked pupillary dilatation in the rat, while PCP and PCP-like drugs are characterized by their ability to produce pupillary constriction in this species.

It should be pointed out that some doubt has been cast over the specificity of the in vitro binding assay²¹ as originally reported by Zukin and Zukin,¹⁷ since PCP has a tendency to adsorb to the glass-fiber filters used in these assays. However, our technique of pretreatment of the filters with *tert*-amyl alcohol reduced binding to the filter by approximately 90%. The residual binding to the filter was nonspecific and was subtracted as part of total nonspecific binding from the total binding to yield specific binding. Vincent et al.²² also have reported techniques for elimination of nonspecific binding to the glass fiber filters.

Experimental Section

Melting points were determined on a Fisher-Johns (hot stage) apparatus and are uncorrected. All new compounds were characterized by melting point, IR, MS, and elemental analysis (C, N, and N). Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN, and were within ±0.3% of the theoretical values. IR spectra were obtained on a Beckman IR-18A using CHCl₃ solutions or KBr pellets. Mass spectra were obtained on a Finnigan Model 3300 quadrupole GC-mass spectrometer operating in the methane chemical-ionization mode and equipped with a Finnigan Model 6000 Interactive Data System.

1-Phenylcyclooctyl Azide (10). A solution of 9²² (5.0 g, 0.025 mol) in 25 mL of CHCl₃ was added slowly with stirring to a solution of sodium azide (3.18 g, 0.049 M) and trichloroacetic acid (8.33 g, 0.049 mol) in 24 mL of CHCl₃ at -5 °C. The temperature was not allowed to exceed 5 °C during the addition. After the addition was complete, the mixture was stirred for 3 h at 0 °C. The solution was neutralized with NH₄OH and extracted with CHCl₃. The CHCl₃ extract was thoroughly washed with H₂O and then dried over Na₂SO₄. The CHCl₃ was evaporated under reduced pressure to yield 4.8 g of a clear viscous liquid: yield 84%; MS, *m/e* (relative intensity) 229 (M⁺, 3), 201 (10), 187 (100). This material was used without further purification.

1-Phenylcyclooctylamine (11). The crude 10 (4.8 g, 0.02 mol) was dissolved in 40 mL of dry ether and added dropwise to a suspension of LiAlH₄ (1.3 g, 0.035 mol) in 100 mL of ether at 0 °C. After the addition was complete, the mixture was refluxed for 2 h. The mixture was cooled to -10 °C, and ethyl acetate-ether (1:1, 26 mL) was slowly added to the mixture. After the evolution of gas ceased, the mixture was poured into an ice-cold solution of 20% HCl. The aqueous portion was collected, neutralized with NH₄OH, and extracted with diethyl ether. The ether solution was washed with a 5% solution of K₂CO₃ and dried over anhydrous Na₂SO₄. Evaporation of the ether gave 2.4 g of a heavy,

- (19) P. Geneste, J. M. Kamenka, M. S. N. Ung, P. Herrman, R. Goudal, and G. Trouiller, *Eur. J. Med. Chem.*, **14**, 301 (1979).
- (20) S. Maayani and H. Weinstein, in "Membrane Mechanisms of Drugs of Abuse", Alan R. Liss, Inc., New York, 1979, pp 91-106.

- (21) S. Maayani and H. Weinstein, *Life Sci.*, **26**, 2011 (1980).
- (22) J. P. Vincent, J. Vignon, B. Kartalovski, and M. Lazdunski, *Eur. J. Pharmacol.*, **68**, 73 (1980).
- (23) A. C. Cope and R. B. Kinnel, *J. Am. Chem. Soc.*, **88**, 752 (1966).

clear, viscous liquid; yield 59%; MS, m/e (relative intensity) 203 (M^+ , 22), 187 (72). This material was used without further purification.

1-(1-Phenylcyclooctyl)piperidine (8) was made by refluxing 11 with 1,5-dibromopentane and K_2CO_3 in DMF: yield 19% (0.69 g); mp 183–185 °C; IR (KBr) 3420, 2940, 3500–3670, 1450, 1205, 1030, 950, 870, 760, 700 cm^{-1} ; MS, m/e (relative intensity) 272 (68), 271 (M^+ , 100). Anal. ($C_{19}H_{30}ClN$), C, H, N.

[3H]PCP Binding Assay. The binding assay was performed as described by Zukin and Zukin.¹⁷ Aliquots of freshly prepared rat brain homogenate (1.0 mL) were incubated at 4 °C for 45 min with 7.0 nM [3H]PCP, and the binding of [3H]PCP to the membrane preparation was measured by filtration assay. The glass-fiber filter was pretreated with water saturated with *tert*-amyl alcohol to reduce binding to the filter. This treatment eliminated approximately 90% of [3H]PCP binding to the glass-fiber filter. The nonspecific binding in the presence of 0.1 mM PCP was subtracted from the total binding to yield specific binding. A concentration-displacement curve for each analogue was visually fitted from a log-probit plot, and the IC_{50} of each analogue was compared to that of PCP, which was used as a standard in each assay.

Discriminative Stimulus Assay. Male, Fischer-derived CDF rats were trained to discriminate between PCP and saline in a two-choice, discrete-trial avoidance task similar to that described in detail elsewhere.⁴ PCP (3.0 mg/kg) or saline was administered intraperitoneally 30 min prior to a training session. Each experimental session consisted of 20 trials, and the rats were trained until they reliably completed at least 90% of the 20 trials on the appropriate choice lever. When acquisition of the discrimination was completed, drug testing sessions were interposed among training sessions. During training sessions, only a response on the appropriate choice lever terminated a trial; during test sessions, a response on either choice lever terminated a trial. A dose of a test drug was considered to produce stimuli which generalized to those produced by PCP if the group of rats completed a mean of at least 90% of the 20 trials on the PCP-appropriate choice lever. Relative potencies were determined by using standard bioassay statistics. PCP produced dose-related discriminative stimuli when tested over a greater than tenfold dose range.

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α -Adrenergic Agents. 1. Direct-Acting α_1 Agonists Related to Methoxamine¹

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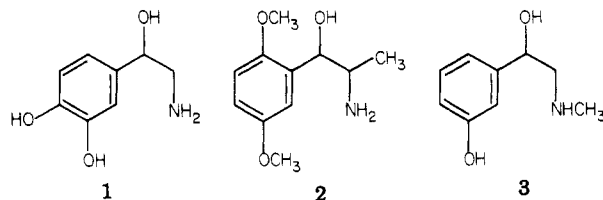
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A series of phenylethylamines related to methoxamine has been prepared and evaluated for direct α_1 -receptor agonist activity. It has been observed that for open-chain compounds such as methoxamine, in which the amine-containing portion is free to adopt numerous conformations, an hydroxyl group is necessary for direct α_1 -adrenergic activity. When the hydroxyl is removed, however, the direct component of activity is greatly reduced unless the amine is incorporated into a more sterically defined structure. From our studies we have concluded that in order for a phenylethylamine to be active as a direct α_1 -receptor agonist it should have a β nitrogen in a fully extended conformation relative to a substituted phenyl ring. For optimum potency, the nitrogen should be exocyclic to a saturated six-membered ring. It may be further incorporated exocyclic or endocyclic into an additional ring so long as the amine occupies a well-defined region of space relative to the aromatic portion of a molecule. The ED_{50} values of some of the more potent compounds as α_1 -receptor agonists are on the order of 1×10^{-7} M.

The phenylethylamines are a well-studied class of pharmacological agents which over the years have been the subject of numerous investigations. In the last decade there have been many studies into the α -adrenergic effects of a variety of phenylethylamines with rigid, as well as flexible, structures²⁻⁸ (and references therein). At the same time, much evidence has been accumulating which indicates that α receptors can be subdivided into at least two pharmacologically distinct classes which can be functionally differentiated by their ability to interact with a series of agonists and antagonists.^{9,10} In addition to the classical

postsynaptic α adrenoceptor (α_1) that mediates the responses of effector organs to norepinephrine, there are also α receptors (α_2) on noradrenergic nerve terminals which modulate the release of norepinephrine in the periphery and the central nervous system.¹¹⁻¹³ This subclassification of α adrenoceptors opens new possibilities for drug discovery through the development of agonists or antagonists having a high degree of selectivity for each receptor subtype.

Norepinephrine (1), the endogenous transmitter of the



sympathetic nervous system, acts with almost equal potency on both α_1 and α_2 receptors.⁹ Other agents, such as methoxamine (2) or phenylephrine (3), are much more specific for the α_1 than for the α_2 receptor and represent attractive points of departure for the development of se-

- (1) This paper has been presented in part. See "Abstracts of Papers", 181st National Meeting of the American Chemical Society, New York, Aug, 1981, American Chemical Society, Washington, DC, 1981, Abstr MEDI 12.
- (2) P. Burn, P. A. Crooks, B. L. Ratcliff, and J. M. H. Rees, *J. Pharm. Pharmacol.*, **32**, 87 (1980).
- (3) G. L. Gruenwald, G. L. Ruth, J. A. Kroboth, T. R. Kamdar, B. V. Patil, and K. N. Salman, *J. Pharm. Sci.*, **65**, 920 (1980).
- (4) H. C. Chang, J. P. Long, D. E. Nichols, and C. F. Barfknecht, *J. Pharmacol. Exp. Ther.*, **188**, 114 (1974).
- (5) D. B. Rusterholz, J. P. Long, J. R. Flynn, and J. R. Glyn, *Arch. Int. Pharmacodyn. Ther.*, **232**, 246 (1978).
- (6) F. M. Sharabi, J. P. Long, D. B. Rusterholz, and C. F. Barfknecht, *Res. Commun. Chem. Pathol. Pharmacol.*, **19**, 1 (1978).
- (7) J. G. Cannon, J. A. Perez, J. P. Pease, J. P. Long, J. R. Flynn, D. B. Rusterholz, and S. E. Dryer, *J. Med. Chem.*, **23**, 745 (1980).
- (8) D. B. Rusterholz, S. E. Dryer, J. P. Long, C. F. Barfknecht, and J. Mott, *Eur. J. Pharmacol.*, **65**, 201 (1980).

- (9) S. Berthelsen and W. A. Pettinger, *Life Sci.*, **21**, 595 (1977).
- (10) C. Melchiorre, *Farmaco, Ed. Sci.*, **35**, 535 (1980).
- (11) S. Z. Langer, *Trends Neurosci.*, **3**, 110 (1980).
- (12) S. Z. Langer, *Br. J. Pharmacol.*, **60**, 481 (1977).
- (13) K. Starke, *Rev. Physiol., Biochem. Pharmacol.*, **77**, 1 (1977).