(Ph); nmr (internal TMS) δ 6.15 (d, 1, J = 8 Hz, 1'-H), 7.13–7.60 (m, 3, Ph), 8.50 (m, 1, H next to Cl on Ph), 8.82 (s, 1, 2-H), 8.87 (s, 1, 8-H), 10.37 (broad, 1, adenine 6-NH), and 12.27 ppm (broad, 1, NH next to Ph). Table II lists the compounds prepared in an analogous manner.

***N*-[9-(β-D-Ribofuranosyl-9*H*-purin-6-yl)carbamoyl]-L-threonine (PCTR, VIa).** A mixture of 33 mg (0.046 mmol) of *N*-[9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl-9*H*-purin-6-yl)carbamoyl]-*O*-benzyl-L-threonine benzyl ester,[5] 50 mg of PdO, and 10 ml of 50% EtOH was hydrogenated at atmospheric pressure for 1 hr. After filtering Pd, the filtrate was evaporated to dryness and the residue stirred in 20 ml of 4 N NH_3–MeOH at room temperature for 6 hr. The solvent was evaporated to dryness and the residue was dissolved in 5 ml of H_2O which was lyophilized. Uv quantitation showed 100% yield. Uv and chromatographic mobilities in various solvent systems were identical with those of the authentic PCTR.

Growth Inhibition. The compounds were tested with cultured cells derived from the buffy coat of a normal individual (Nc 37) and a patient with myeloblastic leukemia (RPMI 6410). Compounds were dissolved in 0.5% DMSO in growth medium (RPMI 1640 + 10% fetal calf serum) at 10^{-4} M (except for **30**, **32**, and **35** which were tested at 5×10^{-5} M because of their limited solubility) and results expressed as per cent of viable cell number relative to control containing 0.5% DMSO after 72 hr of incubation. This DMSO concentration did not alter growth. Tables I and II show the results.

Cytokinin Activity. The compounds were tested for cytokinin activity using a soybean assay previously described.[20,21] The test compounds were dissolved in a minimum quantity of DMSO and then diluted with sterile H_2O. Just prior to solidification of the agar, portions of serial dilutions were added aseptically to 25-ml flasks containing 9 ml of a medium previously described,[20,21] complete except cytokinin. Pieces of soybean tissue (0.5-mg pieces, three per flask) were incubated for 30 days in the dark at 24°. Fresh weights were determined and compared to controls. The lowest concentration of tested compounds that gave a response is used as the criterion for comparing the activities of the analogs. The assays were carried out by Dr. W. H. Dyson in the laboratory of Dr. Ross H. Hall of McMaster University, Hamilton, Ontario, Canada.

Acknowledgment. We wish to thank Dr. A. Mittelman for valuable discussions. We also thank Dr. G. P. Murphy and Dr. E. D. Holyoke for their keen interest and encouragement in this work.

References

(1) C. I. Hong, G. B. Chheda, and S. P. Dutta, 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970, Abstract No. MEDI 55.
(2) G. B. Chheda, R. H. Hall, D. I. Magrath, J. Mozejko, M. P. Schweizer, L. Stasiuk, and P. R. Taylor, *Biochemistry*, **8**, 3278 (1969).
(3) M. P. Schweizer, G. B. Chheda, R. H. Hall, and L. Baczynskyj, *ibid.*, **8**, 3283 (1969).
(4) G. B. Chheda, *Life Sci.*, **8** (2), 979 (1969).
(5) G. B. Chheda and C. I. Hong, *J. Med. Chem.*, 14, 748 (1971).
(6) M. P. Schweizer, K. McGrath, and L. Baczynskyj, *Biochem. Biophys. Res. Commun.*, **40**, 1046 (1970).
(7) G. B. Chheda, "Handbook of Biochemistry," 2nd ed, H. A. Sober, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1971.
(8) R. H. Hall, *Biochemistry*, **3**, 769 (1964).
(9) F. Fittler, L. K. Kline, and R. H. Hall, *ibid.*, 7, 940 (1968).
(10) J. P. Miller and M. P. Schweizer, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, 31, 450 (1972).
(11) R. Thiebé and H. G. Zachau, *Eur. J. Biochem.*, **5**, 546 (1968).
(12) K. Nakanishi, N. Furutachi, M. Funamizu, D. Grunberger, and I. B. Weinstein, *J. Amer. Chem. Soc.*, **92**, 7617 (1970).
(13) R. Gallo, J. Wheing-Peng, and S. Perry, *Science*, **165**, 400 (1969).
(14) J. T. Grace, Jr., M. Hakala, R. H. Hall, and J. Blakeslee, *Proc. Amer. Ass. Can. Res.*, **8**, 23 (1966).
(15) F. Skoog, H. G. Hamzi, A. M. Szweykowska, N. J. Leonard, K. L. Carraway, T. Fujii, J. P. Helgeson, and R. L. Loeppky, *Phytochemistry*, **6**, 1169 (1967).
(16) R. H. Hall and B. I. S. Shrivastava, *Life Sci.*, 7, 7 (1968).
(17) E. Wainfan and B. Landsberg, *FEBS Lett.*, 19, 144 (1971).
(18) A. Divekar and M. T. Hakala, *Mol. Pharm.*, 7, 663 (1971).
(19) G. L. Tritsch, G. B. Chheda, and A. Mittelman, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, 31, 915 (1972).
(20) W. H. Dyson, C. M. Chen, S. N. Alam, R. H. Hall, C. I. Hong, and G. B. Chheda, *Science*, 170, 328 (1970).
(21) W. H. Dyson, R. H. Hall, C. I. Hong, S. P. Dutta, and G. B. Chheda, *Can. J. Biochem.*, **50**, 237 (1972).
(22) J. J. McDonald, N. J. Leonard, R. Y. Schmitz, and F. Skoog, *Phytochemistry*, **10**, 1429 (1971).
(23) S. M. Hecht, R. M. Bock, N. J. Leonard, R. Y. Schmitz, and F. Skoog, *Biochem. Biophys. Res. Commun.*, 41, 435 (1970).
(24) G. Huber, *Angew. Chem.*, **69**, 642 (1957).
(25) A. S. Jones and J. H. Warren, *Tetrahedron*, **26**, 791 (1970).
(26) J. Manning and S. Moore, *J. Biol. Chem.*, **243**, 5591 (1968).
(27) N. J. Leonard, K. L. Carraway, and J. P. Helgeson, *J. Heterocycl. Chem.*, **2**, 291 (1965).
(28) G. B. Chheda and R. H. Hall, *Biochemistry*, **5**, 2082 (1966).
(29) S. M. Hecht and J. J. McDonald, *Anal. Biochem.*, 47, 157 (1972).
(30) G. B. Chheda and R. H. Hall, *J. Org. Chem.*, 34, 3492 (1969).

Potential Anti-Parkinson Drugs Designed by Receptor Mapping

Yvonne C. Martin,* Charles H. Jarboe, Ruth A. Krause, Kathleen R. Lynn, Daniel Dunnigan, and James B. Holland

Experimental Therapy Division, Abbott Laboratories, North Chicago, Illinois 60064. *Received July 24, 1972*

A series of methoxy-1- and -2-aminoindans and aminotetralins as well as 2-oxo-5-amino-1,2,5,6,7,8-hexahydroquinoline was synthesized as potential anti-Parkinson agents. The design of the molecules was based on Kier's receptor mapping technique in that the distances between the heteroatoms of oxotremorine (OT) and dopamine (DA) in reported preferred conformations are similar. None of the compounds antagonized oxotremorine tremors or showed dopaminergic properties. Some of the molecules are analgesics and some are monoamine oxidase inhibitors.

Kier has proposed that drug receptors may be mapped by a comparison of the preferred conformation of several structurally different agonists and/or antagonists to the same receptor. The specific receptor is considered to have sites which interact with those heteroatoms which form a pattern common to all molecules which react with it.[1] Kier also suggested that this technique should be useful in drug design.[1] Since the discovery of novel "leads" remains an important problem in medicinal chemistry, we were eager to evaluate the usefulness of Kier's approach to the design of new drug molecules.

Development of the Model. It has recently been demonstrated that if one increases the body levels of dopamine by administration of its metabolic precursor L-DOPA (3,4-dihydroxyphenylalanine), there is an alleviation of the symptoms of Parkinsonism.[2] Hornykiewicz had previously established that the basal ganglia of Parkinson patients are deficient in dopamine.[3]

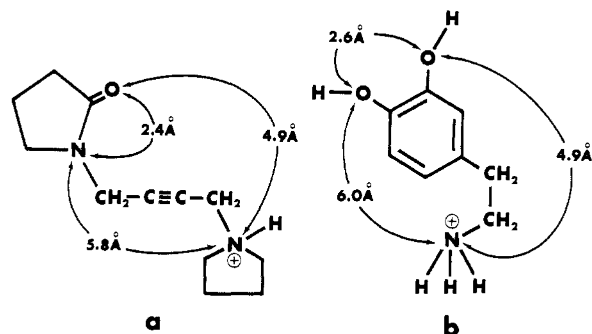

Figure 1. Proposed steric relationship of the essential features of the preferred conformation of oxotremorine (a) and dopamine (gauche conformation) (b).

Table I. Structure of Anti-Parkinson Agents

$R_1C_6H_5COHCH_2CH_2N{=}(CH_2)_n$		
Drug	R_1	n
Trihexylphenidyl	Cyclohexyl	5
Cycrimine	Cyclopentyl	5
Procyclidine	Cyclohexyl	4
Biperiden	5-Norbornen-2-yl	5

Oxotremorine is considered the classic agent for the production of a Parkinsonian-like syndrome in animals.[4] Although the peripheral action of oxotremorine is muscarinic,[5] the tremorigenic properties of oxotremorine are not muscarinic since muscarine and muscarone neither produce nor prevent tremors.[6] DOPA can prevent the tremors produced by oxotremorine.†

The preferred conformation of oxotremorine[7] and dopamine[8,9] has been calculated by extended Hückel theory. The distances between the heteroatoms of these drugs is very similar (Figure 1). Thus it was postulated that dopamine and oxotremorine produce their effects related to tremors by reaction with the same receptor, which is distinct from the muscarinic receptor.

Further Support for the Model. If one cannot isolate a proposed receptor, evidence for the reaction of different drugs with this receptor is at best circumstantial. However, there are experimental observations which support the possibility of the proposed dopamine–oxotremorine receptor which controls tremor. It was previously indicated that DOPA antagonizes oxotremorine tremor.† This effect is even more dramatic when dopamine metabolism is prevented by the administration of the monoamine oxidase inhibitor pargyline.[10]

Atropine abolishes both the biochemical and behavioral effects of oxotremorine.[4] Although atropine is an anticholinergic drug it also inhibits the uptake of dopamine and by this means increases extraneuronal dopamine levels.[11] A molecular model of atropine in a reasonable conformation[12] suggests that it could react with both the proposed muscarinic receptor and the dopamine receptor under consideration here.

Prior to L-DOPA use, four drugs commonly used for the treatment of Parkinsonism were substituted 3-amino-1-phenyl-1-propanols (Table I).[5] Models of these molecules suggest possible interaction with both the muscarinic and the dopaminergic receptors. These drugs are inhibitors of dopamine uptake into corpus striatum synaptosomes.[13]

Therefore, the pharmacology of Parkinsonism treatment as well as its simulation in the laboratory appears to be accommodated by the postulated receptor map. The critical test of the usefulness of the hypothesis then becomes if it can be used to design active antioxotremorine or dopaminergic drugs.

Design of New Molecules. The proposed receptor map was used to design potential anti-Parkinson drugs as different from dopamine and oxotremorine as possible yet with the appropriate distances fixed in a rigid molecule. The final choice of molecules was based on synthetic ease and the proper partition coefficient. The compounds are listed in Table II. All except one are phenethyl- or benzylamines. The nitrogen, oxygen, and a carbon atom of the aromatic ring would presumably engage the receptor. In compound **18** the heteroatoms are the same as those in oxotremorine.

Since the compounds chosen are also related to the *N,N*-dimethyl-2-aminotetralins which have analgesic properties,[14] such testing was also performed. Oxotremorine has analgesic properties which are antagonized by DOPA.[15] Thus the proposed receptor map might apply to analgesic as well as antitremor properties.

Results

Analgesic Activity. These results are listed in Table III. Several molecules are active. The common feature of all active compounds (**1, 2, 11, 13, 14,** and **17**) is a N to O distance of 6.4 Å, whereas in the two classes which contain no active compounds (**5–9** and **15**) the corresponding distance is approximately 6 Å. The distance between the nitrogen and the allylic hydroxyl oxygen of morphine is 6.5 Å. However, it is also clear that this distance is not common to all analgesics.[16]

Dopaminergic Activity. The results of the pharmacological tests are summarized in Table IV. None of the compounds antagonized oxotremorine (OT) tremors, limb abduction, or salivation. Compounds **1** and **5** abolished the diarrhea produced by OT, and compound **2** increased activity. None of the compounds antagonized the deserpidine-induced depression.

Most of the drugs are potent monoamine oxidase inhibitors *in vitro* and some are active *in vivo* (these properties will be discussed in a subsequent publication).

This report thus documents an attempt to use Kier's receptor mapping technique[1] to design dopaminergic compounds for synthesis. It did not seem to improve the efficiency of discovery of new drug "leads" in the area of dopaminergics. The basic deficiencies in the method are that (1) the drugs chosen for the model may not react in an identical manner with the receptor; (2) rather than heteroatoms the "common" atoms might be carbon atoms of a specific stereochemical and electronic nature; (3) the molecules designed to test the relationship might contain atoms which prevent proper drug-receptor interactions; and (4) conformational mobility of the drug might be necessary to produce the desired effect.[17]

Experimental Section

Synthesis. Ketones. 5,6-Dimethoxy-1-indanone, 6-methoxy-1-tetralone, 5-methoxy-2-tetralone, and 5-methoxy-1-tetralone were purchased from Aldrich Chemical Co., Milwaukee, Wis. 4-Methoxy-1-indanone,[18] 2,5-dioxo-1,2,5,6,7,8-hexahydroquinoline,[19] and 5-methoxy-1-indanone[20] were prepared by literature methods.

6-Hydroxy-1-tetralone was prepared by a 4-hr hydrolysis (steam bath) of 17.6 g of 6-methoxy-1-tetralone in 75 ml of glacial acetic acid plus 75 ml of 48% HBr. After cooling 16 hr the mixture was poured over ice to precipitate, yield 95% (crude).

†G. M. Everett, personal communication.

Table II. Summary of Syntheses

I II III IV

No.	Type	R	X	Y	Z	Method of prepn	Formula[a]	Recrystn solvent	Mp of HCl salt, °C	% yield
1	I	H	H	MeO	H	IA	$C_{11}H_{15}NO \cdot HCl$	$EtOH-Et_2O$	258-260	52
2	I	Me	H	MeO	H	II	$C_{12}H_{17}NO \cdot HCl$	$MeOH-Et_2O$	205	47
3	I	Me	H	HO	H	II	$C_{11}H_{15}NO \cdot HCl$[b]	$EtOH-Et_2O$	205-207	63
4	I	*i*-Pr	H	MeO	H	III	$C_{14}H_{21}NO \cdot HCl$[c]	$EtOH-Et_2O$	184-185	72
5	I	H	H	H	MeO	IA	$C_{11}H_{15}NO \cdot HCl$	Et_2O	>250	60
6	I	Me	H	H	MeO	II	$C_{12}H_{17}NO \cdot HCl$	$EtOH-Et_2O$	208 dec	27
7	I	Me	H	H	HO	II	$C_{11}H_{15}NO \cdot HCl$	$C_6H_5Me-EtOH$	244-246	42
8	I	*i*-Pr	H	H	MeO	III	$C_{14}H_{21}NO \cdot HCl$	*i*-PrOH	212-213.5	82
9	I	$CH_2C_6H_5$	H	H	MeO	IV	$C_{18}H_{21}NO \cdot HCl \cdot H_2O$	*d*	83.5-86	55
10	II	H	H	H	MeO	IB	$C_{11}H_{15}NO \cdot HCl$[e]	$EtOH-Et_2O$	250 dec	22
11	II	Me	H	H	MeO	II	$C_{12}H_{17}NO \cdot HCl$[f]	*i*-PrOH	204-207	18
12	III	H	H	MeO	H		$C_{10}H_{12}NO \cdot HCl$[g]			
13	III	Me	H	MeO	H	II	$C_{11}H_{15}NO \cdot HCl$	$MeOH-Et_2O$	148	?
14	III	*i*-Pr	H	MeO	H	III	$C_{13}H_{19}NO \cdot HCl$	*d*	225-226	60
15	III	H	H	H	MeO	IA	$C_{10}H_{13}NO \cdot HCl$	*d*	200-205	39
16	III	Me	MeO	MeO	H	II	$C_{12}H_{17}NO_2 \cdot HCl$	MeOH-EtOH	200	74
17	III	*i*-Pr	MeO	MeO	H	III	$C_{14}H_{21}NO_2 \cdot HCl$[h]	*d*	>210	50
18	IV	H	H	H	H	V	$C_9H_{12}N_2O \cdot HCl$	MeOH-*i*-PrOH	236-237	56

[a]Analysis for C, H, and N ±0.4% except where indicated. [b]*Anal.* H; C: calcd, 61.8; found, 62.7; N: calcd, 6.6; found, 5.8. [c]*Anal.* H, N; C: calcd, 65.7; found, 66.2. [d]Product crystallized from reaction mixture. [e]D. E. Ames, D. Evans, T. F. Grey, P. J. Islip, and K. E. Richards, *J. Chem. Soc.*, 2636 (1965), report mp 258-260°. *Anal.* H, N; C: calcd, 61.8; found, 61.1. [f]See reference in footnote *e*, no melting point. *Anal.* H, N; C: calcd, 63.2; found, 62.6. [g]K. V. Lershina, A. I. Gavrilova, and S. I. Sergievskaya, *Zh. Obshch. Khim.*, **30**, 3634 (1960). (Our sample was obtained from the Abbott collection.) [h]*Anal.* H, N; C: calcd, 61.9; found, 61.2.

Table III. Analgesic Properties of the Drugs in the Mouse Tail-Pinch Test

Compd no.	Dose, mg/kg ip	Response time of treated / Response time of control
1	100	>5
2	100	2
3	30	0.4
4	30	0.3
5	30	0.8
6	30	1.0
7	100	0.7
8	30	0.4
9	100	0.2
10	30	0.4
11	10	>6
13	100	2.0
14	100	>5
15	30	1.0
16	30	>4
17	100	0.4
Codeine sulfate	50	3.0
Dextropropoxyphene[a]	30	10.0

[a]Darvon.

5-Hydroxy-1-tetralone was hydrolyzed as above. The mixture was poured into boiling H_2O. The product crystallized on cooling, yield 51% (crude).

Aminoindans and Aminotetralins. I. Primary Amines. Method A. A mixture of *ca.* 10 g of ketone, 7 g of $NH_2OH \cdot HCl$, 1 ml of C_6H_5N, and 50 ml of CH_3OH was allowed to react at room temperature for 4 hr. The oxime crystallized when chilled. The oxime precursor of compound **15** was recrystallized from $C_2H_5OH-H_2O$; others were used in crude form. A suspension of 0.025-0.10 mol of oxime, 10 g of KOH, 9 g of Raney Ni, and 150 ml of CH_3OH was reduced under 3 atm of H_2 until the theoretical equivalents of H_2 had been absorbed.

Method B. A suspension of 5 g of ketone, 100 ml of C_2H_5OH, 10 ml of anhydrous NH_3, and 1 g of 5% Pd on C was reduced as above.

II. Methylamines. A tenfold excess of CH_3NH_2 was allowed to react for 1-2 hr with 0.025-0.10 mol of ketone in CH_3OH. The resulting solution of Schiff base was reduced as above using 20-30 wt % of 5% Pt on C catalyst.

III. Isopropylamines. The corresponding primary amine in CH_3OH or C_2H_5OH was allowed to react for 1-2 hr with a sixfold excess of acetone. The resulting solution of Schiff base was reduced in the same way as the methylamines.

IV. Benzylamine. A mixture of 7.6 g of compound **5** plus 10 g of benzaldehyde in 100 ml of CH_3OH was allowed to react 2 hr and then reduced as above using 1.5 g of prewashed Raney Ni catalyst.

Product Isolation. After reduction the catalyst was filtered off and washed with H_2O. Except where KOH was used in the reaction the wash plus reaction mixture was evaporated to dryness and recrystallized. If the product was the free base, HCl was added to the recrystallization solvent. When KOH had been used in the reduction the wash plus reaction mixture was concentrated under reduced pressure to remove solvent and then the product was extracted into Et_2O. The Et_2O was then evaporated and the product was recrystallized from solvent containing HCl.

2-Oxo-5-amino-1,2,5,6,7,8-hexahydroquinoline (18). The oxime was prepared by refluxing (2 hr) a solution of 10 g of 2,5-dioxo-1,2,5,6,7,8-hexahydroquinoline, 12 g of $NH_2OH \cdot HCl$, and 35 g of 40% $KOH-H_2O$ in 70 ml of C_2H_5OH. The solution was concentrated, diluted with H_2O, and acidified with concentrated HCl. The resulting oxime hydrochloride was recrystallized from dimethylformamide-diethyl ether (mp 310-312°). The oxime was reduced by method A above. The catalyst was removed by filtration, and solvent was evaporated. The resulting crude amine was dissolved in H_2O; the solution was acidified to pH 2.5 with HCl and applied to a column of acid-washed IR-200. The amine was eluted with 6 *N* NH_4OH. The eluate was evaporated and dissolved in HCl, and the product recrystallized from $CH_3OH-CH_3CHOHCH_3$.

Pharmacology. Oxotremorine (OT) Antagonism. A dose of the drug close to the LD_{50} was used. Groups of ten mice were given drugs intraperitoneally (ip). Thirty minutes later an ip dose of 0.5 mg/kg of OT sesquifumarate (Aldrich) was administered; 15 min after this injection each mouse was graded on a 1-3 scale for tremors, limb abduction, activity, salivation, and diarrhea. No deaths occurred within this 45 min. The score reported in Table IV is the sum of the response of all ten mice of that group. The salivation response to OT varied; thus these results are reported as per cent of control. A control (OT alone) group was included in each study. The score of normal mice is also included for comparison.

Reversal of Deserpidine Depression. This was evaluated by their ability to antagnoize the depression produced 24 hr after a

Table IV. Antagonism of the Pharmacological Effects of Oxotremorine by the Drugs[a]

Drug	Dose, mg/kg	Tremor	Limb abduction	Activity	Salivation[b]	Diarrhea
None		0	0	10	0	0
Oxotremorine		25 ± 3	24 ± 2	2 ± 2	100	22 ± 4
Oxotremorine + **1**	30	24	25	2	130	5
Oxotremorine + **2**	30	20	16	8	67	19
Oxotremorine + **3**	30	25	27	1	90	26
Oxotremorine + **4**	10	26	25	3	144	24
Oxotremorine + **5**	30	30	28	3	70	4
Oxotremorine + **6**	30	24	22	2	85	17
Oxotremorine + **7**	100	26	25	2	78	22
Oxotremorine + **8**	10	26	24	3	100	24
Oxotremorine + **9**	100	27	27	0	91	23
Oxotremorine + **10**	1	25	25	2	69	26
Oxotremorine + **11**	10	23	23	1	100	23
Oxotremorine + **12**	10	25	25	2	100	23
Oxotremorine + **13**	30	27	27	1	70	22
Oxotremorine + **14**	30	27	23	4	73	25
Oxotremorine + **15**	30	26	25	1	123	22
Oxotremorine + **16**	10	24	24	1	85	26
Oxotremorine + **17**	100	27	26	1	119	24
Oxotremorine + **18**	100	27	26	1	69	23
Oxotremorine + 1-DOPA	400	13	11	15	185	6
Oxotremorine + atropine	0.3	15	14	8	0	0
Oxotremorine + cycrimine	30	6	0	10	0	1

[a]The numbers reported are the total scores on an arbitrary scale for the group of ten mice. [b]Per cent of control.

50 mg/kg oral dose of deserpidine (free base). The test drugs were administered to groups of ten mice ip at a dose of 100 mg/kg if this was tolerated (no deaths) or 25 mg/kg if a lower dose was necessary. They were observed for 30–60 min. The monoamine oxidase inhibitor pargyline (200 mg/kg) is inactive in this test whereas DL-DOPA (800 mg/kg) restores normal activity.

Tail Pinch Antinociceptive Test. Compounds were tested at 100 mg/kg ip unless they caused deaths at that dose; in such cases the highest tolerated dose was used. After dosing (30 min) a standard clamp is placed on the tail of the mouse. The number of seconds which elapse before the mouse bites the clamp is recorded. If the average time of the three mice to bite is double the control or greater, the compound is considered to be an analgesic. Very potent analgesics abolish the response altogether.

Physical Properties. The distances were measured on Dreiding models constructed according to the preferred conformations reported[7-9] or to the possible conformation described in the discussion.

Acknowledgments. Dr. G. M. Everett's consultation on the pharmacology and biochemistry of Parkinsonism was especially helpful.

References

(1) L. B. Kier in "Fundamental Concepts in Drug-Receptor Interactions," J. F. Moran and D. J. Triggle, Ed., Academic Press, New York, N. Y., 1970, pp 15–45.
(2) G. C. Cotzias, M. H. van Wuert, and L. M. Schiffer, *N. Engl. J. Med.*, **276**, 374 (1967).
(3) O. Hornykiewicz in "Biochemistry and Pharmacology of the Basal Ganglia," E. Costa, L. J. Cote, and M. D. Yahr, Ed., Raven Press, Hewlett, N. Y., 1965, p 171.
(4) A. H. Friedman and G. M. Everett, *Advan. Pharmacol.*, 3, 83 (1964).
(5) A. K. Cho, W. L. Haslett, and D. J. Jenden, *J. Pharmacol. Exp. Ther.*, 138, 249 (1962).
(6) L. S. Goodman and A. Gilman, "The Pharmacological Basis of Therapeutics," 3rd ed, Macmillan, New York, N. Y., 1953, p 473.
(7) L. B. Kier, *J. Pharm. Sci.*, **59**, 112 (1970).
(8) L. B. Kier and E. B. Truitt, Jr., *J. Pharmacol. Exp. Ther.*, 174, 97 (1970).
(9) T. Bustard and R. Egan, *Tetrahedron*, **27**, 44 (1971).
(10) G. M. Everett and B. Bopp, *Pharmacologist*, 8, 184 (1966).
(11) M. Goldstein, K. Fuxe, A. F. Battista, T. Backstrom, and A. Nakatani, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **29**, 280 (1970).
(12) L. G. Abood in "Drugs Affecting the Central Nervous System," Vol. 2, A. Burger, Ed., Marcel Dekker, New York, N. Y., 1968, pp 128, 158.
(13) J. T. Coyle and S. H. Snyder, *Science*, **166**, 899 (1969).
(14) A. R. Martin, A. P. Parulkar, D. J. Gusseck, L. J. Anderson, G. L. Grunewald, and A. I. White, *J. Pharm. Sci.*, **58**, 340 (1969).
(15) B. J. Pleuvry and M. A. Tobias, *Brit. J. Pharmacol.*, **43**, 706 (1971).
(16) P. S. Portoghese, *J. Pharm. Sci.*, **55**, 865 (1966).
(17) P. S. Portoghese, *ibid.*, **60**, 806 (1971).
(18) J. D. Loudon and R. K. Razdan, *J. Chem. Soc.*, 4299 (1954).
(19) G. R. Pettit, W. C. Fleming, and K. D. Paull, *J. Org. Chem.*, **33**, 1089 (1968).
(20) C. Panetta and S. Bunce, *ibid.*, **26**, 4859 (1961).