Stereochemical Studies on Medicinal Agents. V.[1] Synthesis, Configuration, and Pharmacological Activity of Pipradrol Enantiomers

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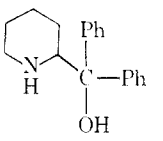
Enantiomers of pipradrol were synthesized from (*R*)- and (*S*)-pipecolic acid and the probable conformation of the base was deduced through ir studies. It was determined that all of the central stimulant activity resided in (*R*)-pipradrol, and that both the (*R*) and (*S*) isomers possessed anticonvulsant properties. The fact that the more active enantiomers of pipradrol and amphetamine are not configurationally related suggests that the mode of action of these central stimulants may differ, and this is in agreement with recent work which has shown that (*R*)-pipradrol is direct acting while amphetamine and the ephedrines act by an indirect mechanism. The stereospecificity of pipradrol and the much lower steric requirements for indirect-acting, central stimulants has led to the generalization that direct action factors a higher degree of stereoselectivity than indirect action.

There appears to be no consistent relationship between absolute stereochemistry and central stimulant activity. For example, while it is known[2] that (*S*)-(+)-amphetamine[3] (I) possesses greater central activity than its antipode, a recent study[4] has indicated that (−)- and (+)-ephedrine (II) are about equipotent and exhibit greater central activity than optical antipodes of ψ-ephedrine (III). The fact that the ephedrines contain two asymmetric centers further obscures any correlation between absolute stereochemistry and central effect, insofar as relating activity to the configuration of a specific asymmetric center is concerned.

I

II, *erythro*
III, *threo*

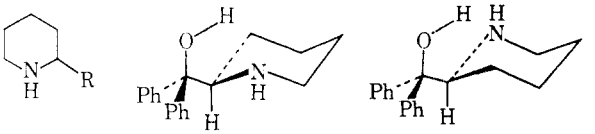
In an effort to assess the importance of steric factors, it was of interest to investigate other enantiomeric CNS stimulants containing a single asymmetric center, since this would eliminate the number of variables associated with such correlations and might provide valuable information concerning their mode of action. For example, if the more active enantiomers of two central stimulants are not configurationally related, this might suggest that the divergence in stereochemical requirements is related to dissimilar modes of action. This could involve an indirect mechanism[5] or direct interaction with central adrenergic receptors. It was our objective to prepare enantiomers of the CNS stimulant, pipradrol (IV),[6,7] from configurationally known starting material in order to ascertain whether a



IV

stereochemical relationship exists between the more active enantiomers of amphetamine and pipradrol.

Chemistry.—The enantiomers of pipradrol were synthesized from optically active pipecolic acids (V) of known configuration.[8] The resolution of pipecolic acids was carried out by a modification of the procedures described in the literature.[9] Each of the antipodes of pipecolic acid was converted to the corresponding methyl ester hydrochloride (VI·HCl) by Fischer esterification. The salts were employed as such in the Grignard reaction, rather than as free bases, in order to minimize the possibility of diketopiperazine formation. Addition of finely pulverized VI·HCl to excess phenylmagnesium bromide in ether yielded the optical isomers



V, R = COOH
VI, R = COOMe

IVa, (*R*)

IVb, (*S*)

of pipradrol (IVa and IVb) which were isolated as the hydrochloride salts and free bases. Results from one of our laboratories showed that good yields of pipradrol antipodes were also obtainable from the freshly prepared free amino esters (VI). In accordance with the

(1) Previous paper: P. S. Portoghese, *J. Med. Chem.*, **10**, 1057 (1967).

(2) J. W. Schulte, E. C. Reif, J. A. Bacher, Jr., W. S. Lawrence, and M. L. Tainter, *J. Pharmacol. Exptl. Therap.*, **71**, 62 (1941).

(3) P. Karrer and K. Ehrhardt, *Helv. Chim. Acta*, **34**, 2202 (1951); J. Kenyon, *et al.*, *J. Chem. Soc.*, 1072 (1935), and papers in this series; P. A. Levine and A. Walti, *J. Biol Chem.*, **90**, 81 (1931); A. W. Schrecker, *J. Org. Chem.*, **22**, 33 (1957).

(4) G. Lanciault and H. H. Wolf, *J. Pharm. Sci.*, **54**, 84 (1965), and references cited therein.

(5) R. J. Wurtman, "Catecholamines," Little, Brown and Co., Boston, Mass., 1966.

(6) C. H. Tilford, R. S. Shelton, and M. G. Van Campen, *J. Am. Chem. Soc.*, **70**, 4001 (1948); F. J. McCarty, C. H. Tilford, and M. G. Van Campen, *ibid.*, **79**, 472 (1957).

(7) B. B. Brown and H. W. Werner, *J. Pharmacol. Exptl. Therap.*, **110**, 180 (1954).

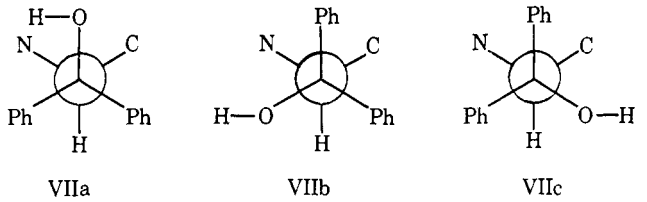
(8) F. E. King, T. J. King, and A. L. Warwick, *J. Chem. Soc.*, 3590 (1950).

(9) J. P. Greenstein and M. Winitz, "Chemistry of Amino Acids," Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1961, p 2538.

synthetic scheme, the (+)-base and (−)-hydrochloride salt were derived from (*R*)-(+)-pipecolic and hence have the (*R*) configuration (IVa). Conversely, the (−)-base and (+)-hydrochloride salt are in the (*S*) series (IVb).

The infrared spectrum (Figure 1) of pipradrol in tetrachloroethylene[10] at 0.005 *M* showed a band at 3450 cm^{-1} which is characteristic[11] of intramolecular, O–H···N bonding. The fact that no band could be detected in the vicinity of 3600 cm^{-1} indicates the absence of any significant quantity of free hydroxyl. The sharp, medium-intensity peak at 3315 cm^{-1} was in the range of the N–H stretching vibrational frequency.[12] At high concentration (0.5 *M*) both the OH and NH absorptions were at frequencies identical with those found in the high-dilution studies. There were, however, several very low-intensity bands between 3150 and 3300 cm^{-1} which were not observed at low concentration and which may be due to the presence of a small amount of intermolecularly bonded[13] species.

The infrared data suggest that pipradrol possesses strong intramolecular hydrogen bonds. If it is assumed that the piperidine ring is in a chair conformation which is stabilized by an equatorial diphenylcarbinol group, three staggered conformations (VII) are possible. Conformation VIIc can be eliminated as a significant contributor to the rotameric population because intramolecular hydrogen bonding in this rotamer is unlikely. Of the remaining internally bonded species, rotamer VIIa should be more thermodynamically favored be-



VIIa VIIb VIIc

cause the axial, C-2 ring proton is flanked by the two bulky phenyl moieties. This is clearly a lower energy conformation than that in which the aromatic groups flank the C-3 atom of the piperidine ring as shown in VIIb. On this basis it is proposed that pipradrol consists primarily of rotamer VIIa and is best represented by stereoformula IVa or IVb.

Pharmacology.—The effect of racemic and optically active pipradrol on spontaneous, coordinated motor activity in mice was measured using the photocell counter technique of Dews.[14] In Figure 2 the average activity of groups of five mice each are represented graphically in terms of the number of times the mice broke a light beam in their cage during a period of 90 min following oral administration of various doses of these compounds. The activity of control animals is included in the area enclosed by the dashed lines.

The signs of CNS activity with orally administered, racemic pipradrol are motor stimulation with doses above 3 mg/kg. Motor activity increases with increasing dose until it reaches a peak at about 17 mg/kg. With higher doses, incoordinated activity and ataxia occur, followed by tremors and clonic convulsions. The same symptoms occur with (*R*)-pipradrol in doses approximately half those of the racemate. No CNS stimulation was seen with (*S*)-pipradrol.

These experiments indicate that all of the central, stimulant activity of the racemate resides in the (*R*) isomer (IVa).[15] Estimation of the dose–effect curve on the basis of the content of active enantiomer in the racemate revealed that the calculated curve closely approximated that of the (*R*) isomer. This suggests that, in addition to being devoid of stimulant activity, (*S*)-pipradrol does not significantly antagonize the

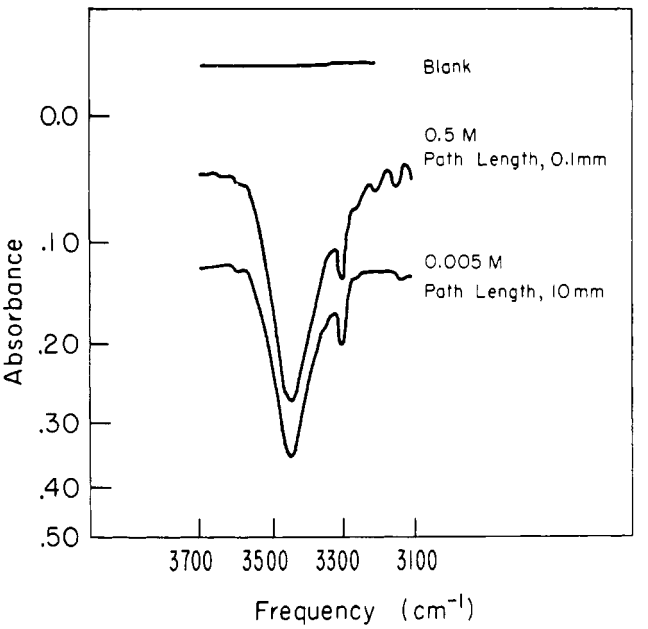


Figure 1.—Infrared spectra in the hydroxyl region for pipradrol in tetrachloroethylene solvent.

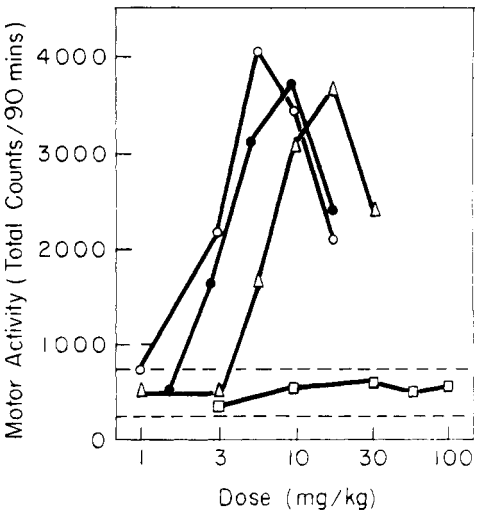


Figure 2.—The effect of racemic pipradrol (Δ), (*R*)-pipradrol (○), and (*S*)-pipradrol (□) on spontaneous motor activity of mice after oral administration. Note that the curve (●) which was calculated from values of the racemate closely approximates the experimentally determined curve for (*R*)-pipradrol. The activity of control animals is included in the area enclosed by the dashed lines.

(10) It was found that $CHCl_3$, CCl_4, and CS_2 were unsuitable as solvents because they reacted with pipradrol.

(11) T. Kanzawa, *Bull. Chem. Soc. Japan*, **29**, 398, 479 (1956); G. Hite, E. E. Smissman, and R. West, *J. Am. Chem. Soc.*, **82**, 1207 (1960).

(12) R. A. Russell and H. W. Thompson, *J. Chem. Soc.*, 483 (1955).

(13) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., p 253.

(14) P. B. Dews, *Brit. J. Pharmacol.*, **8**, 46 (1953).

(15) Intraperitoneal administration of racemic and optically active pipradrol also showed the (*R*) isomer to possess all of the motor simulant activity.

effect of the (*R*) isomer. It was demonstrated further that (*S*)-pipradrol had no significant effect on (+)-amphetamine-induced stimulation in mice with doses of 30–55 mg/kg.

It was determined that the anticonvulsant activity which has been previously reported[7,16] for *racemic* pipradrol is retained by both isomers. The anticonvulsant activity was evaluated by its ability to antagonize the tonic-extensor component of electroshock-induced seizures in mice. Orally, the ED_{50} of (*S*)-pipradrol was 38 ± 3 mg/kg and that for the (*R*) isomer was 55 ± 7 mg/kg.

Discussion.—A high order of stereoselectivity[17] is, in many cases, not associated with centrally acting drugs. For example, amphetamine (I) exhibits a low degree of stereoselectivity amounting to only a fourfold[2] difference in activity between (+) and (−) isomers. A similar situation has been found with ephedrine (II) in that both enantiomers have about equal potency.[4] This is also true for optical isomers of ψ-ephedrine (III).[4]

The foregoing examples do not suggest any apparent coherent relationship between absolute stereochemistry and central-stimulant activity. The lack of correlation is made still more apparent in the case of pipradrol where we have found all of the central-stimulant activity associated with the (*R*) isomer (IVa) while the more active enantiomer[2] of amphetamine [(*S*)-(+)-I] possesses the opposite configuration.[3]

Recent investigations by Wolf[18] and Weisman[19] and their co-workers on the mode of action of these CNS stimulants reveal a possible explanation for these results. It has been found that the central effects of enantiomeric amphetamines[18,19] and ephedrines[18] can be blocked by pretreatment with α-methyltyrosine, a potent inhibitor of catecholamine biosynthesis. This has given support to the idea that these compounds exert their central effects in an indirect fashion by releasing catecholamines. In contrast to this, the CNS stimulation produced by (*R*)-pipradrol was not affected significantly by α-methyltyrosine.[18] This suggests that the CNS-stimulant action of (*R*)-pipradrol is predominantly a direct effect and is consistent with the fact that there is no stereochemical relationship between the more active enantiomers of pipradrol and amphetamine. (*R*)-Pipradrol most likely functions as a stimulant by interacting with receptors having steric requirements which differ from those involved in the release of endogenous catecholamines.[20]

The pattern which emerges from the above data suggests that indirect-acting CNS stimulants generally have lower stereochemical requirements while direct action favors a higher degree of stereoselectivity. The obvious implication[20] of such a generalization is that the receptors which are directly involved in the mediation of a CNS response have a molecular architecture which is more demanding than those associated with the release of catecholamines. However, it should be emphasized that receptor stereoselectivity should also be dependent on the molecular constitution of the stimulant. Thus, an overlapping spectrum of enantiomeric potency ratios may emerge for direct- and indirect-acting stimulants, with the indirect-acting compounds generally showing potency ratios which are closer to unity.

It is of interest that (*S*)-pipradrol, which is completely devoid of stimulant effect, has anticonvulsant activity. The fact that there is no apparent antagonism between (*R*)- and (*S*)-pipradrol indicates that these enantiomers are acting on different receptors in the CNS. The lack of stimulant activity or antagonism of the (*S*) isomer might possibly be a reflection of the absence of both intrinsic activity and affinity[21] for the receptors.

Experimental Section[22]

(*R*)-Pipecolic Acid [(*R*)-V].—An aqueous solution (120 ml) containing 18.45 g (0.15 mole) of picolinic acid and 24.18 g (0.16 mole) of (+)-tartaric acid was shaken with 0.5 g of PtO_2 at an initial H_2 pressure of 3.52 kg cm² (50 psi) until the theoretical amount of H_2 was absorbed. The mixture was freed from the catalyst by filtration and the solvent was removed *in vacuo*. Recrystallization of the crude salt yielded material whose physical constants agree with those reported.[23]

The salt (16.9 g, 0.057 mole) in 1 l. of H_2O was passed through an HOAc-treated IR-45 column. After removal of solvent from the eluate and crystallization from EtOH–EtOAc, there was obtained 7.1 g of (*R*)-pipecolic acid whose physical constants agree with literature[23] values.

(*S*)-Pipecolic Acid [(*S*)-V].—The mother liquor from the preparation of (*R*)-pipecolic acid (+)-tartrate was diluted with 3 l. of H_2O and passed through a column containing HOAc-treated IR 45 resin. The solvent from the eluate was removed *in vacuo*, and the residue was dissolved in 200 ml of EtOH containing 15.0 g (0.10 mole) of (−)-tartaric acid to give 15.6 g of the tartrate salt. Treatment of this salt in the above manner yielded 6.9 g of (*S*)-V, whose physical constants agreed with those reported.[23]

Methyl Pipecolate Hydrochloride (VI·HCl).—Dry HCl was passed for 0.5 hr into 100 ml of absolute MeOH containing 6.6 g (0.05 mole) of optically active pipecolic acid. The solvent was removed *in vacuo* and the residue crystallized from MeOH–EtOAc to yield 5.6 g of product, mp 168–170°. The values of $[\alpha]^{23}D$ (*c* 10, H_2O) for VI·HCl derived from (*R*)-V and (*S*)-V were +6.9 and −6.9°, respectively.

Anal. Calcd for $C_7H_{14}NO_2Cl$: C, 46.84; H, 7.86; N, 7.81; Cl, 19.8. Found: C, 46.85; H, 7.98; N, 7.34; Cl, 20.5.

(*R*)- and (*S*)-Pipradrol (IVa and IVb).—To 140 ml of ethereal phenylmagnesium bromide prepared from 3.9 g (0.16 g-atom) of Mg and 25 g (0.16 mole) of bromobenzene was added slowly, 3.6 g (0.02 mole) of powdered (*R*)-VI with constant stirring. The mixture was refluxed for 1.5 hr, then poured into ice-cold, dilute HCl. The aqueous phase was separated, extracted with EtOAc, made alkaline with 1 *N* NaOH, and ex-

(16) D. L. Braun and B. B. Brown, *J. Pharmacol. Exptl. Therap.*, **119**, 135 (1957).

(17) The term "stereoselectivity" signifies that pharmacological activity is found predominantly, though not exclusively, in one isomer while "stereospecificity" implies that activity resides only in one isomer. This definition is adapted from E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 436.

(18) H. H. Wolf, private communication; H. H. Wolf, D. E. Rollins, and C. R. Rowland, 114th Meeting of the A.Ph.A., 1967, Academy of Pharmaceutical Sciences, Abstracts, p 92.

(19) A. Weisman, B. K. Koe, and S. S. Tenen, *J. Pharmacol. Exptl. Therap.*, **151**, 339 (1966).

(20) While secondary effects such as differences in metabolism, distribution, and excretion cannot yet be ruled out for pipradrol enantiomers, it presently appears that the observed stereospecificity[17] is most reasonably ascribed to events at the receptor level. For example, (+)- and (−)-metha done differ greatly in their analgetic activity, although only minor differences were noted in the distribution, metabolism, and excretion of each antipode [C. Y. Sung and E. L. Way, *ibid.*, **109**, 244 (1953)].

(21) E. J. Ariens, "Molecular Pharmacology," Vol. I, Academic Press Inc., New York, N. Y., 1964, p 183.

(22) Melting points, determined with a Thomas–Hoover capillary melting point apparatus, are uncorrected. The routine infrared spectra were obtained with a Perkin-Elmer 237B spectrophotometer (KBr disk). The high-resolution spectra were carried out in tetrachloroethylene solution on a Perkin-Elmer 621 machine. The nmr data were obtained with the Varian A-60 spectrometer using D_2O as solvent and 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt as internal standard. Specific rotations were determined with a Perkin-Elmer 141 polarimeter.

(23) H. C. Beyerman, *Rec. Trav. Chim.*, **78**, 137 (1959); A. V. Robertson and L. Marion, *Can. J. Chem.*, **37**, 829 (1959).

tracted once again with EtOAc. The solvent was removed *in vacuo*, and the oily residue was treated with ethereal HCl. After two crystallizations from EtOH–Et_2O, there was obtained 3.66 g of IVa·HCl, mp 288–289° dec, $[\alpha]^{25}D$ −63.6° (*c* 1, H_2O). Employing (*S*)-VI in an identical procedure afforded 3.8 g of IVb·HCl, mp 287–288° dec, $[\alpha]^{25}D$ +66.9° (*c* 1, H_2O). The infrared spectra of both anitpodes were identical with the optically active salts obtained by optical resolution.[24] The nmr spectrum exhibited multiplet resonances at 2 (6 H, $(CH_2)_3$), 3.5 (2 H, NCH_2), 4.4 (1 H, NCHCO), and 7.7 (*W* = 16 cps, 10 H, Ar) ppm.

The bases were generated from the purified hydrochloride salts by treatment with 1 *N* NaOH and were recrystallized from Skelly B to give crystals, mp 97–98°, $[\alpha]^{25}D$ +59.8° (IVa) and −57.9° (IVb) (*c* 2, MeOH). The high-resolution infrared spectrum of IV at 0.5 and 0.005 *M* concentrations showed bands at 3450 (O–H···N) and 3315 cm^{-1} (NH).

Acknowledgment.—The authors are grateful to Dr. H. H. Wolf of the College of Pharmacy, Ohio State University, who informed us of the results of his studies on the effect of α-methyltyrosine on CNS activity of pipradrol and ephedrine isomers.

(24) (+)-Pipradrol dibenzoyl-(+)-tartrate neutral salt monohydrate was obtained from a MeOH solution of 2 equiv of pipradrol[6] and 1 equiv of resolving acid; mp 138–142°, $[\alpha]^{25}D$ −69° (*c* 2, MeOH). (−)-Pipradrol dibenzoyl-(+)-tartrate neutral salt was crystallized from either MeOH (10–15 ml/g) or 95% EtOH (20–25 ml/g); mp 170–172°, $[\alpha]^{25}D$ −36° (*c* 2, MeOH). The two salts were converted to the optically active bases which were recrystallized from 75–90° petroleum ether to give (+)-pipradrol (IVa), mp 98–100°, $[\alpha]^{25}D$ +58.5° (*c* 2, MeOH), and (−)-pipradrol (IVb), mp 95–97°, $[\alpha]^{25}D$ −62.5° (*c* 2, MeOH). The two bases were converted to the HCl salts which were purified by recrystallization from either 95% EtOH or a mixture of MeCOEt–MeOH; IVa·HCl, mp 303–305° dec, $[\alpha]^{25}D$ −68.8°, and IVb·HCl, mp 305–307° dec, $[\alpha]^{25}D$ +68.5° (*c* 2, H_2O). The melting points of the HCl salts, determined by the customary capillary tube method, are decomposition points which are quite variable and depend upon the rate of heating. The (*R*) and (*S*) enantiomers employed in the pharmacological studies were obtained by the above procedure (private communication from E. R. Andrews and P. L. Tiernan, The Wm. S. Merrell Company, and J. L. Schaar, currently at Monsanto Research Corp., Dayton, Ohio).

Enzyme Inhibitors. XIX. The Synthesis of Some 1-Hydroxy-2-hydroxymethyl-4-(6-substituted-9-purinyl)cyclohexanes as Nucleoside Analogs[1a]

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The syntheses of some 1-hydroxy-2-hydroxymethyl-4-(6-substituted-9-purinyl)cyclohexanes were accomplished by the following procedure. Diethyl 4,4-ethylenedioxypimelate on Dieckmann cyclization gave 2-carbethoxy-4,4-ethylenedioxycyclohexanone. Catalytic hydrogenation of the ketone followed by $LiAlH_4$ reduction of the ester gave 2-hydroxymethyl-4,4-ethylenedioxycyclohexanol which after several additional reactions was separated into *trans*- and *cis*-3-acetoxymethyl-4-acetoxycyclohexanes (**5a** and **5b**). Hydrogenation of the ketone group of **5a** and **5b** gave the alcohols which were converted into tosylates. Displacement of the tosylate with azide followed by catalytic hydrogenation of the azides gave the amines. The major product from **5a** was 1α-amino-3α-hydroxymethyl-4β-hydroxycyclohexane, whereas **5b** gave nearly an equal mixture of 1α- and 1β-amino-3α-hydroxymethyl-4α-hydroxycyclohexanes. The stereochemistry of these trisubstituted cyclohexanes was deduced from nmr studies. Finally two of these amines were converted into some 1β-hydroxy-2α-hydroxymethyl-4α-(6-substituted-9-purinyl)cyclohexanes and 1α-hydroxy-2α-hydroxymethyl-4α-(6-amino-9-purinyl)-cyclohexane. These compounds were not potent inhibitors of adenosine deaminase, possibly because they are repelled by the hydrophobic region of this enzyme.

In several previous studies, it was found that certain 9-(substituted cyclopentyl)- and 9-(substituted cyclohexyl)adenines were capable of inhibiting the enzyme, adenosine deaminase. For example, if an OH group were located on the 2 position of the cyclopentyl or cyclohexyl group, it was found that this substitution increased inhibition relative to the unsubstituted cycloalkyl group.[2] However, if an OH group were located at position 3 of the cyclohexyl group or if a hydroxymethyl group were located at position 4 of the cycloalkyl group, little change in inhibition of adenosine deaminase was noted relative to 9-cyclopentyladenine.[3,4] Based on this and other data,[5] it was concluded that the 2-OH group of these inhibitors makes a contribution to binding to adenosine deaminase. In order to determine the effect on inhibition of adenosine deaminase by certain 9-cyclohexyl-6-substituted purines that contain both an OH group and a hydroxymethyl group on the cyclohexyl moiety, we decided to prepare some 1-hydroxy-2-hydroxymethyl-4-(6-substituted-9-purinyl)cyclohexanes. This paper describes the synthesis, stereochemistry and enzymatic evaluation of these compounds.

Chemistry.—Our main goal in this area was to develop a general route for the preparation of 1-hydroxy-2-hydroxymethyl-4-(6-substituted-9-purinyl)-cyclohexanes which could later be applied to each of the four possible isomers. For the sake of simplicity, no consideration will be given to the stereochemistry of the intermediates in the procedure outlined in Chart I. However, the separation of isomers and their identification will be described in the following section. Dieckmann cyclization of diethyl 4,4-ethylenedioxypimelate (**1**) by a modification of a previously reported

(1) (a) This investigation was supported by Grant T-337A from the American Cancer Society, by research Grant 5-R01-GM-09775-05 from the Public Health Service, by research career program award 5-K3-CA-18718-05 from the National Cancer Institute, and training Grant 5-T1-GM-555-05 from the Division of Medical Sciences, U. S. Public Health Services, Bethesda, Md. (b) National Merit Winner, Lunsford Richardson Award.

(2) H. J. Schaeffer, S. Marathe, and V. Alks, *J. Pharm. Sci.*, **53**, 1368 (1964).

(3) H. J. Schaeffer, K. K. Kaistha, and S. K. Chakraborti, *ibid.*, **53**, 1371 (1964).

(4) H. J. Schaeffer, D. D. Godse, and G. Liu, *ibid.*, **53**, 1510 (1964).

(5) H. J. Schaeffer, D. Vogel, and R. Vince, *J. Med. Chem.*, **8**, 502 (1965).