In another run, 7.3 g of the enamine was taken through this reaction sequence without the isolation or purification of any intermediates. The gum which was obtained following the last step was chromatographed on Florisil. Recrystallization of the crystalline fractions from cyclohexane gave 3.3 g of **14**, mp 140–143°.

3,4-Diphenyl-2-methyl-3-cyclohexen-1-one (15).—A mixture of 3.0 g of the enamine and 2 ml of MeI in 20 ml of DMF was stirred under N_2 at room temperature for 18 hr. Water (100 ml) was added, and stirring was continued for 3 hr. Ether was added, and the organic layer was washed well (H_2O, brine). The solid which remained when the solvent was removed was recrystallized twice from ligroin to give 1.2 g of **15**, mp 66–70°, ν_{max} 1705 cm^{-1}, doublet at δ 1.16.

Anal. Calcd for $C_{19}H_{18}O$: C, 86.98; H, 6.94. Found: C, 86.98; H, 7.17.

5,6-Diphenyl-4a-methyl-4,4a,7,8-tetrahydro-2(3H)-naphthalenone (16).—A solution of 1.19 g of the cyclohexenone **15**, 0.500 ml of methyl vinyl ketone, and 20 ml of benzene was added during 30 min to a suspension of methanol-free NaOCH$_3$ (from 0.10 g of Na metal) in 10 ml of benzene. After 2 hr (stirring) at room temperature and 1 hr at reflux, the mixture was worked up as in the case of **10**. The residual gum was chromatographed over Florisil (elution with 2.5% acetone in ligroin). The crystalline fractions were recrystallized twice from MeOH to afford 0.72 g of **16**, mp 131–134°, λ_{max}^{abs} 238 mμ (ε 19,800).

Anal. Calcd for $C_{23}H_{22}O$: C, 87.86; H, 6.85. Found: C, 87.54; H, 6.85.

Stereochemical Aspects of Analgesics. Preparation of 10-Methyl-5-phenyl-5-propionoxy-*trans,syn,trans*-tetradecahydroacridine[1]

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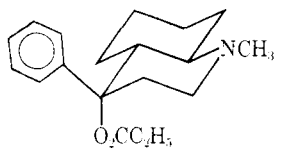
Received May 2, 1967

10-Methyl-5(e)-phenyl-5(a)-propionoxy-*trans,syn,trans*-tetradecahydroacridine (**13a**) was prepared by the reaction of 10-methyl-*trans,syn,trans*-dodecahydroacridone (**11**) with phenyllithium followed by esterification of the resulting alcohol, **12a**. The compound was tested for analgesic activity and was found inactive.

It has been shown that there is relatively no difference in analgesic activity between the rigid analogs of prodine, the 1-methyl-4-phenyl-*trans*-decahydro-4-propionoxyquinolines (**1** and **2**).[3] Beckett, in his original postulate of the analgesic receptor site, proposed a



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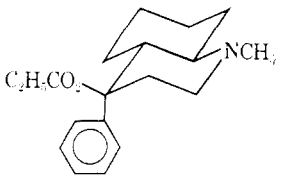

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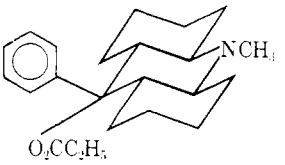
three-point receptor, modeled on the morphine molecule,[4] which required an axial disposition of the phenyl ring, an amino group, and a two-carbon chain to fit a receptor-site cavity. The piperidine ring of prodine- or meperidine-type analgesics can be substituted with small alkyl functions and still fit such a cavity.

The purpose of this work was to design an analgesic in which large bulky groups were placed in the 2, 3, 5, and 6 positions of the piperidine nucleus of a prodine-type system and to maintain rigid conformations of the phenyl and ester functions at the 4 position. The molecule selected for this purpose was 10-methyl-5-phenyl-5-propionoxy-*trans,syn,trans*-tetradecahydroacridine with the phenyl being equatorial (**3**) and axial (**4**).

Bell and Archer have reported ethyl 3-α-phenyltropane-3-β-carboxylate (**5**) to be slightly more active than meperidine.[5] However, in this system there is



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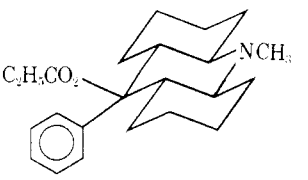

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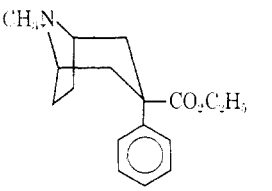

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no unequivocal control of the conformation of the phenyl ring and no steric barrier to the approach of the phenyl ring to the receptor site.

In analogy to the preparation of the 1-methyl-4-phenyl-*trans*-decahydro-4-propionoxyquinolines (**1** and **2**),[3] it was assumed that the axial and equatorial isomers of 10-methyl-5-phenyl-5-hydroxy-*trans,syn,trans*-tetradecahydroacridine (**12a** and **e**) could be obtained by the reaction of the corresponding acridone **11** with either phenyllithium or phenylmagnesium bromide (Chart I). The scheme devised for the preparation of 10-methyl-*trans,syn,trans*-dodecahydroacridone (**11**) involved the reduction of anthranilic acid (**6**). The catalytic reduction of **6** utilizing 5% rhodium on alumina had been reported but solvent conditions were not specified.[6] Freifelder[7] had reported that pyridinealkanoic acids could be reduced in dilute aqueous ammonia and this solvent system was found to be useful for the reduction of anthranilic acid.

(1) Taken in part from the dissertation presented by Martin Steinman, June 1965, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Ph.D. degree.

(2) National Institutes of Health Predoctoral Fellow, 1964–1965.

(3) E. E. Smissman and M. Steinman, *J. Med. Chem.*, **9**, 455 (1966).

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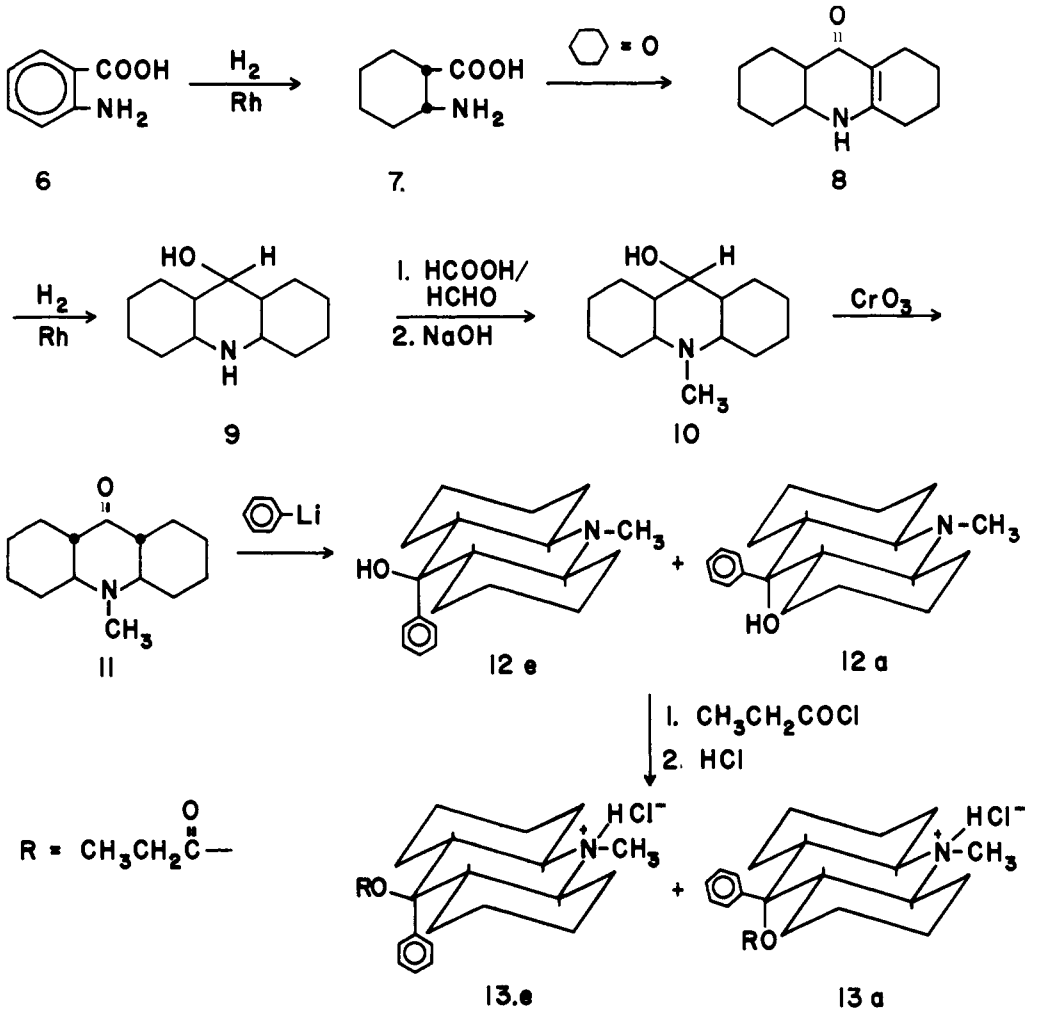
CHART I



The decahydroacridone **8** was reportedly made from *trans*-hexahydroanthranilic acid in unstated yield.[8] In the present work a similar procedure utilizing *cis*-hexahydroanthranilic acid (**7**) was found to be satisfactory; Perkin reported the melting point of the decahydroacridone **8** as 275° and this was the melting point obtained when the *cis* acid was employed. Thus it appears that either *cis*- or *trans*- hexahydroanthranilic acid leads to the same product. Perkin and Sedgwick[8] attempted to reduce **8** by an electrolytic method, but not enough material was available for investigation of the product. The reduction of **8** was unsuccessful with 5% Pd–C in absolute alcohol at ambient pressure or 3.52 kg/cm^2; it was likewise unsuccessful with PtO_2 in absolute alcohol. Upon reduction of **8** with 5% Rh–Al, tetradecahydro-5-hydroxyacridine (**9**) was obtained. An Eschweiler–Clarke methylation of **9** yielded the formate ester of the desired 10-methyltetradecahydro-5-hydroxyacridine (**10**) and hydrolysis with aqueous sodium hydroxide yielded **10**. Oxidation of the resulting alcohol produced the perhydroacridone **11**.

That the perhydroacridone **11** is the *trans,syn,trans* compound is indicated by several lines of evidence. In the nmr the lowest field absorption was due to the N-methyl group at δ 2.42. It would be expected that an equatorial methine proton adjacent to a nitrogen or a carbonyl would occur at lower field than the N-methyl protons. Also, the infrared spectrum showed the Bohlmann bands which require the methine protons adjacent to nitrogen to be axial.[9] The crude mixture, obtained after the reaction, was allowed to stand overnight in methanolic sodium methoxide. It was analyzed by glpc and indicated no change in the mixture of starting material and product. The oxidation was performed in strong acid and in the isolation procedure the material was made strongly basic; thus, there was opportunity for the ketone to epimerize to the most stable isomer by either acid or base catalysis. An excellent review of the steric configuration of piperidine derivatives provides many examples which substantiate the above assignment.[10]

The perhydroacridone failed to react with phenylmagnesium bromide, and in the reaction with phenyllithium only one of the isomeric alcohols could be found by glpc and chromatography on alumina. Numerous attempts to obtain two isomers from this reaction by varying the reaction conditions failed to produce the desired results. The steric barrier to an axial approach of the phenyl function in this reaction prevented the formation of the equatorial alcohol **12e**.

The only isomer obtained from the phenylation reaction, 10-methyl-5(e)-phenyl-5(a)-hydroxy-*trans,syn,*-

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trans-tetradecahydroacridine (**12a**), was esterified by the method of deStevens.[11] The esterification failed by the method of Ziering[12] and Beckett[13] (propionic anhydride and pyridine) and also by the method of Blicke[14] in which the hydrochloride salt of the amino alcohol is treated with propionic anhydride.

The resulting axial ester **13a** was submitted for testing by the Eddy hot plate method[15] using subcutaneous administration. The compound was inactive at doses of 20, 50, and 100 mg/kg and at the last dose was convulsive.

No definite conclusions can be offered from these data. However, since it has been shown previously that the conformation of the phenyl ring in prodine analogs is apparently not important, the supposition can be offered that the tetradecahydroacridines would behave similarly to the decahydroquinolines if the substituted two-carbon chain was not important to receptor-site fit. Since no activity was observed, the bulky group substituted on the two-carbon chain must be important or could be altering transport to the effector site.

Experimental Section[16]

***cis*-Hexahydroanthranilic Acid (7).**—Anthranilic acid (30 g, 0.219 mole, Eastman, recrystallized) was dissolved in 200 ml of water and 12 ml of concentrated NH_3 and was hydrogenated at 3.37 kg/cm² with 7 g of 5% Rh–Al. The reduction was 80% complete in 24 hr after which time no more H_2 was absorbed. After removal of the catalyst, the solvent was evaporated and the compound was recrystallized from aqueous Me_2CO to yield 18.8 g (60%) of **7**: mp 234° (lit.[6] mp 232–233° dec); infrared (KBr) 3.30–4.83 and 6.10 (NH_3^+), 6.35 (CO_2^-); nmr (CF_3CO_2H), complicated multiplet 1.50–3.00 (CH_2), two multiplets centered at 3.53 and 4.08 (C–H), and a broad band centered at 7.35 (NH_3^+).

1,2,3,4,6,7,8,9,5a,9a-Decahydroacridone (8).—*cis*-Hexahydroanthranilic acid (**7**) (8.2 g, 0.057 mole) was mixed with cyclohexanone (8.0 g, 0.082 mole). The mixture was heated at 130° for 2 hr and at 240° for an additional 2 hr, during which time the evolution of NH_3 could be detected. The mass was extracted with hot water to remove unreacted acid and recrystallized from EtOH and Me_2CO to yield 5.4 g (46%) of product: mp 275°; ir (KBr), 3.06 and 3.28 (secondary amide vinylog[17]), 6.22 (C=O), and 6.35–6.65 (α,β-unsaturated β-amino C=O[18]); uv, λ_{max}^{EtOH} 323 mμ (ε 11,800); nmr (CF_3CO_2H), three broad bands 0.70–1.60, 1.65–2.40, and 2.60–3.30.

Perkin reports the same melting point for the decahydroacridone made from *trans*-hexahydroanthranilic acid.[8]

Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 75.69; H, 9.41; N, 7.12.

Tetradecahydro-5-hydroxyacridine (9).—The decahydroacridone **8** (4.7 g, 0.023 mole) was hydrogenated in 80 ml of AcOH with 1 g of 5% Rh–Al. Hydrogen absorption was complete in 4 hr. The uv spectrum was obtained in order to observe the absence of the absorption at 323 mμ for the starting material; in cases in which the absorption was still present, the hydrogenation was continued after the addition of more catalyst. AcOH was evaporated and the remaining material was made basic with saturated aqueous K_2CO_3. The mixture was extracted with five portions of $CHCl_3$, the solution was dried ($MgSO_4$) and filtered, and the $CHCl_3$ was evaporated. The material was recrystallized from benzene and petroleum ether to yield 3.6 g (75%) of product: mp 209–212°; ir (KBr), 3.07 (N–H) 9.58 and 9.87 (C–O stretching of equatorial alcohol[19]); nmr ($CDCl_3$), envelopes at 0.90–2.05 and 2.05–2.50, peaks at 1.84, 2.22, and 2.42, broad band from 2.70–3.20 (1 H).

Anal. Calcd for $C_{13}H_{23}NO$: C, 74.64; H, 10.89; N, 6.59. Found: C, 74.59; H, 11.08; N, 6.69.

10-Methyltetradecahydro-5-hydroxyacridine (10).—The methylation of the secondary amine **9** was performed by modification of known procedures.[20,21] Tetradecahydro-5-hydroxyacridine (**9**) (8.9 g, 0.043 mole) was mixed with 98% formic acid (4.5 ml, 1.2 moles) with cooling, followed by the addition of 15 ml (0.02 mole) of 35% formalin solution. The mixture was placed in an oil bath (90–100°) for a few minutes until gas evolution began. The flask was removed from the oil bath for 15 min and then replaced in the oil bath (95–100°) for 8 hr. At the end of this time the formic acid was evaporated and 15% NH_4OH was added until the solution became alkaline. The solution was extracted with five portions of $CHCl_3$), dried ($MgSO_4$), and filtered, and the $CHCl_3$ was evaporated. An oil remained which was the formate ester of the desired compound: ir (liquid film), 5.80 (C=O), 8.10, 8.50, and 8.73 (ester C–O stretching).

The formate ester was hydrolyzed according to the method of Oliveto and co-workers.[22] It was dissolved in 325 ml of MeOH and 60 ml of 1 *N* NaOH was added. The solution was stirred at room temperature overnight. The MeOH was evaporated and the solution was extracted (five portions of $CHCl_3$). The $CHCl_3$ solution was dried ($MgSO_4$) and filtered, and the solvent was evaporated. This material in 1:1 petroleum ether (60–68°)–acetone with several drops of MeOH was passed through 10 g of alumina; upon evaporation of the solvent the product precipitated; yield 8.3 g (87%); mp 105–106° (after recrystallization from petroleum ether); ir (KBr), 9.54 and 9.78 (C–O stretching for equatorial alcohol[19]), no absorption at 3.07 μ (N–H); nmr ($CDCl_3$), broad peak 3.41 (>CHO–), broad envelope 0.80–2.15, and 2.18 (N–CH_3).

Anal. Calcd for $C_{15}H_{25}NO$: C, 75.28; H, 11.28; N, 6.27. Found: C, 75.30; H, 11.04; N, 6.32.

10-Methyl-*trans,syn,trans*-dodecahydroacridone (11).—10-Methyltetradecahydro-5-hydroxyacridine (**10**) (8.25 g, 0.37 mole) was oxidized according to Willstätter's method.[23] Chromic acid (2.46 g, 0.037 equiv) in 2.4 ml of H_2O and 12 ml of AcOH was added over a period of 3 hr to a well-stirred solution of the alcohol in 100 ml of AcOH; the solution of the alcohol was heated at 60–70°. After the addition of the chromic acid was completed, the mixture was heated a short time and most of the AcOH was evaporated. The solution was made strongly basic with 32% NaOH and extracted (Et_2O). The ether solution was dried ($MgSO_4$), filtered, and evaporated. Upon recrystallization from EtOAc–petroleum ether (60–68°), 1 g of product was obtained. The remaining crude oil (4.5 g) was chromatographed on 100 g of Woelm alumina (grade III) using 1:1 EtOAc–petroleum ether. Fractions (25 ml) were collected and the first three contained the ketone (4.2 g): total yield 5.2 g (63%); mp 110–111° (after recrystallization from EtOAc–petroleum ether (60–68°)); ir (KBr), 3.60 with shoulder on the high wavelength side (Bohlmann bands),[9] 5.88 (C=O); the spectrum in $CHCl_3$ showed the absence of an alcohol function; nmr ($CDCl_3$), broad envelope 0.90–2.40, peak 2.42 (N–CH_3).

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(23) R. Willstätter, *Ber.*, **29**, 393, 936 (1896).

Anal. Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 75.52; H, 10.30; N, 6.36.

10-Methyl-5(e)-phenyl-5(a)-hydroxy-*trans,syn,trans*-tetradecahydroacridine (12a).—The reaction of the ketone **11** (0.50 g, 0.0023 mole) with phenyllithium was performed according to the procedure of Ziering[12] and Beckett.[13] Li (0.64 g, 0.092 g-atom) was placed in 100 ml of dry ether. A few drops of bromobenzene was added, and the mixture warmed to start the reaction. The remaining bromobenzene (a total 0.8 g, 0.0046 mole) was added at a rate to cause the mixture to reflux vigorously. After the addition was complete, the mixture was refluxed an additional 45 min. The flask was cooled in an ice–salt water bath, the ketone **11** was added over 10 min, and the mixture was stirred at room temperature for 2 hr, refluxed for 1 hr, and allowed to stand for 5 hr. HCl was added while the mixture was cooling in an ice bath. The ether layer was separated, and the aqueous layer was made alkaline with concentrated NH_4OH and extracted five times with 50-ml portions of ether. The ether layers were combined, dried ($MgSO_4$), and filtered, and the ether was removed to give the desired product (**12a**) in 66% (0.45 g) yield, mp 165° (recrystallized from Me_2CO); ir (KBr), 9.52 and 9.84 (C–O stretching of alcohol[19]), 14.24 (phenyl), (in $CHCl_3$) 2.77 (OH); nmr (CCl_4), envelope 0.80–2.20, 2.21 (N–CH_3), broad band 7.20–7.60 (aromatic).

Anal. Calcd for $C_{20}H_{29}NO$: C, 80.22; H, 9.76; N, 4.68. Found: C, 79.96; H, 9.94; N, 4.62.

10-Methyl-5(e)-phenyl-5(a)-propionoxy-*trans,syn,trans*-tetradecahydroacridine Hydrochloride (13a).—The alcohol **12a** (1.4 g, 0.0047 mole) in 50 ml of dried toluene was added slowly to freshly distilled propionyl chloride (2.0 g, 0.0216 mole) in 15 ml of dried toluene. The mixture was stirred and heated at 60–70° for 7 hr. At the end of this time the precipitate was made alkaline with aqueous $NaHCO_3$ and extracted ($CHCl_3$). The $CHCl_3$ solution was dried and the solvent was evaporated to yield 0.7 g of starting alcohol.

The toluene solution was evaporated and the remaining material was made alkaline with aqueous $NaHCO_3$. The material was extracted ($CHCl_3$) and the latter solution was dried. Upon evaporation of the chloroform, the ester was prepared to yield 0.65 g of product (71% over-all yield from alcohol based on material consumed); mp 109–111° (after purification with activated charcoal in Me_2CO and precipitation of the salt from an acetone solution with ether); ir (KBr), 5.78 (C=O); nmr ($CDCl_3$), broad envelope 0.80–3.35 with a triplet centered at 1.28 (ester CH_3), quartet center at 3.82 (ester CH_2), broad band 4.84, broad band 7.30–7.90 (aromatic).

Anal. Calcd for $C_{23}H_{34}NO_2Cl$: C, 70.47; H, 8.74; N, 3.57. Found: C, 69.98; H, 8.94; N, 4.09.

Acknowledgment.—The authors gratefully acknowledge the support of this project by the National Institutes of Health Grants RG-9254 and MH-20,887. The authors wish to express their appreciation to Dr. Everette L. May, Mrs. Louise Atwell, and Mrs. Wendy Ness of the Section of Medicinal Chemistry, Laboratory of Chemistry, National Institute of Mental Disease, for performing the animal tests and probit analyses, and for private communications concerning their research.

Stereochemical Studies on Medicinal Agents. IV.[1] Conformational Analysis of Ephedrine Isomers and Related Compounds

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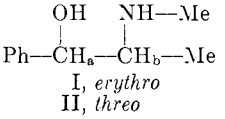
The conformational preference of ephedrine isomers has been deduced from nmr studies of these compounds and the corresponding 3-methyl-2-phenylmorpholine diastereomers. The nmr data suggest that, in a variety of solvents, the ephedrines are intramolecularly hydrogen bonded both as the free bases and salts. A possible explanation for the stereo structure–activity relationship of the ephedrines has been advanced. Arylethanolamines such as epinephrine and other related physiologically active compounds have been suggested to exist primarily as internally hydrogen-bonded species.

The differences in activity between ephedrine and its optical isomers have received considerable attention[2] and the conformational aspects of these compounds with respect to their biological activity recently have been discussed.[3] Although the complete stereochemistry of ephedrine (I) and ψ-ephedrine (II) has been established rigorously,[4,5] an assignment of the conformational preference of these diastereomers has remained somewhat controversial. Based on differences in reactivity, it was believed that ephedrine and ψ-ephedrine resided in two different conformations.[6,7]



I, *erythro*
II, *threo*

It was later suggested[8–10] that a *gauche* and *trans* relationship existed for the hydroxyl and methylamino groups in ψ-ephedrine and ephedrine, respectively. Everett and Hyne[11] reached the same conclusion from a study of the dissociation constants of isomeric ephedrinium ions. Based on infrared studies, Kansawa[12] proposed that both isomers are in *gauche* conformations in chloroform and carbon tetrachloride. In this connection, however, it was noted that ψ-ephedrine formed stronger intramolecular hydrogen bonds. More recently, Hyne[13] has investigated the

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