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.

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

PHILIP S. PORTOGHESE

Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota 55455

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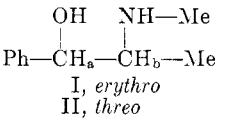
The conformational preference of ephedrine isomers has been deduced from nmr studies of these compounds and the corresponding 3-methyl-2-phenylmorpholine diastereomers. The nmr data suggest that, in a variety of solvents, the ephedrines are intramolecularly hydrogen bonded both as the free bases and 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

(1) Previous paper, P. S. Portoghese and T. N. Riley, *J. Pharm. Sci.*, **54**, 1831 (1965).

(2) (a) K. K. Chen, C. K. Wu, and E. Henriksen, *J. Pharmacol Exptl. Therap.*, **36**, 363 (1929); (b) K. Shimamoto, S. Uchizumi, and O. Kanauchi, *Japan. J. Pharm. Chem.*, **27**, 460 (1955); (c) R. A. Hahn, J. B. LaPidus, A. Tye, and J. W. Nelson, *J. Pharm. Sci.*, **54**, 378 (1965); (d) P. N. Patil, A. Tye, and J. B. Lapidus, *J. Pharmacol. Exptl. Therap.*, **148**, 158 (1965); (e) G. Lanciault and H. H. Wolf, *J. Pharm. Sci.*, **54**, 841 (1965).

(3) R. B. Barlow, "Introduction to Chemical Pharmacology," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1964, p 310; J. B. Lapidus, A. Tye, P. Patil, and B. A. Modi, *J. Med. Chem.*, **6**, 76 (1963).

(4) K. Freudenberg, E. Schoffel, and E. Braun, *J. Am. Chem. Soc.*, **54**, 234 (1932); K. Freudenberg and F. Nikolai, *Ann.*, **510**, 223 (1934).

(5) D. C. Phillips, *Acta Cryst.*, **7**, 159 (1954).

(6) H. Emde, *Helv. Chim. Acta*, **12**, 365 (1929).

(7) W. N. Nagai and S. Kanoa, *Ann.*, **470**, 157 (1929).

(8) L. H. Welsh, *J. Am. Chem. Soc.*, **71**, 3500 (1949).

(9) W. J. Close, *J. Org. Chem.*, **15**, 1131 (1950).

(10) G. Fodor and K. Koczka, *J. Chem. Soc.*, 850 (1952).

(11) D. H. Everett and J. B. Hyne, *ibid.*, 1936 (1958).

(12) T. Kansawa, *Bull. Chem. Soc. Japan*, **29**, 398 (1956); **29**, 479 (1956); **29**, 604 (1956).

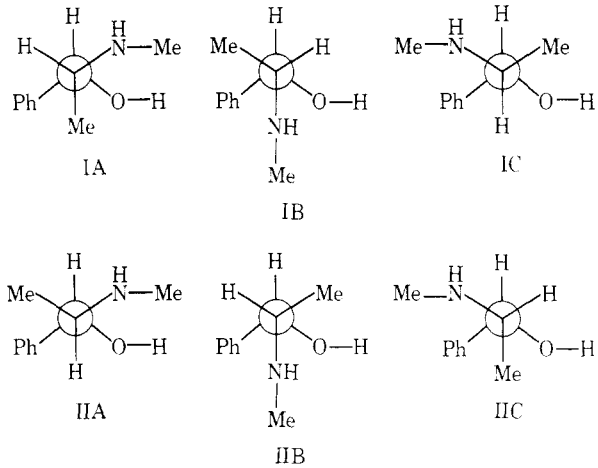
(13) J. B. Hyne, *Can. J. Chem.*, **38**, 125 (1960).

ephedrines by means of nmr and has provided additional evidence that the ψ-base is more strongly internally hydrogen bonded. It subsequently was suggested[14] that ephedrine and ψ-ephedrine exist in "off staggered" conformations. This was based on the assumption that the vicinal spin–spin coupling constant (J_{ab}) of the ψ-base, according to the Karplus[15] relationship, was related to a dihedral angle of approximately 150°. With ephedrine base, J_{ab} = 4 cps was equated with a dihedral angle of 80–90°. It is now known that factors other than dihedral angle may influence the magnitude of vicinal coupling and Karplus[16] recently has commented on the dangers of deriving such information from coupling constants. Thus, it has been shown that electronegativity of substituents[17,18] as well as the configuration of electronegative groups[19,20] may cause significant changes in the value of J_{vic}. For these reasons J_{vic} cannot be employed as a means of quantitatively determining dihedral angle unless it is compared with a closely related compound of known conformational preference.

In view of the above discrepancies regarding the conformational preference of ephedrine and ψ-ephedrine, an nmr reinvestigation of these diastereomers was conducted together with parallel studies on closely related model compounds (III and IV) possessing fewer degrees of rotational freedom. Moreover, as there is no reported nmr study on the conformational preference of the protonated forms of I and II, and since it is possible that the pharmacologic effects are mediated *via* the ionized species, the salts of these compounds were also investigated.

Results and Discussion

Coupling Constants.—Ephedrine (I) and ψ-ephedrine (II) each can exist in three possible staggered conformations (A, B, and C). Since the rate of interconversion



between these rotamers is large compared to the nmr frequency, the vicinal coupling constant, J_{ab}, represents a weighted average of all conformations. For this reason, we thought it advantageous to investigate appropriate model compounds in conjunction with studies on I and II. The *cis* and *trans* isomers of 3-methyl-2-phenylmorpholine[21] (III and IV, respectively) appeared well suited for this purpose since the morpholine ring should exist in a chair conformation.[20,22]

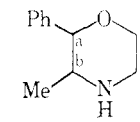
TABLE I

H_aH_b COUPLING CONSTANTS OF ISOMERIC EPHEDRINE AND RELATED MORPHOLINE BASES

	J_{ab}			J_{ab}		
Solvent	I	II	ΔJ_{ab}[a]	III	IV	ΔJ_{ab}[b]
CCl_4	...	...	...	3.05	8.96	5.91
C_6H_6	3.76	7.98	4.22	3.16	9.12	5.96
$CDCl_3$	4.07	8.23	4.16	2.99	8.80	5.81
DMSO	4.26	7.89	3.63	2.95	8.70	5.75

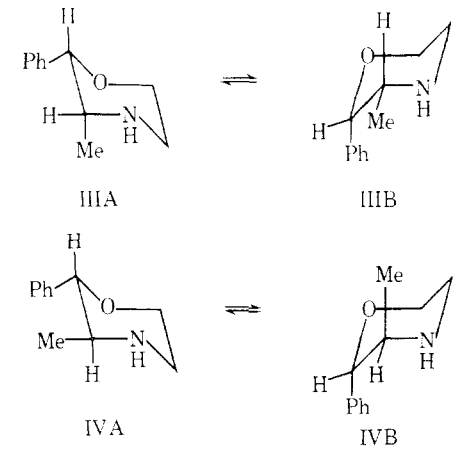
[a] $II_{J_{ab}} - I_{J_{ab}} = \Delta J_{ab}$. [b] $IV_{J_{ab}} - III_{J_{ab}} = \Delta J_{ab}$.

The values of J_{ab} for III and IV (Table I) are close to 3 and 9 cps, respectively, and are consistent with a *gauche* disposition between H_a and H_b for the former and an antiparallel orientation for the latter compound. The small variations in J_{ab} which take place in different solvents may possibly arise largely from factors



III, *cis*
IV, *trans*

other than changes in conformational equilibria. This is suggested by the observation that J_{IV}–J_{III} = ΔJ_{ab} is fairly constant in solvents of widely differing polarity.

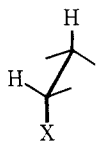


If the geometry of the morpholine ring[20,22] is similar to that of the chair form of cyclohexane, it should be possible to calculate approximate values of ΔG for the equilibria, IIIA ⇌ IIIB and IVA ⇌ IVB, from known values for substituents found in the literature.[23]

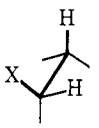
(14) J. B. Hyne, *Can. J. Chem.*, **39**, 2536 (1961).
(15) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).
(16) M. Karplus, *J. Am. Chem. Soc.*, **85**, 2870 (1963).
(17) P. Laszlo and P. von R. Schleyer, *ibid.*, **85**, 2709 (1963).
(18) K. L. Williamson, C. A. Lanford, and C. R. Nicholson, *ibid.*, **86**, 762 (1964).
(19) D. H. Williams and N. S. Bhacca, *ibid.*, **86**, 2742 (1964).
(20) H. Booth, *Tetrahedron Letters*, 411 (1965); H. Booth and G. C. Gidley, *Tetrahedron*, **21**, 3429 (1965).
(21) F. H. Clarke, *J. Org. Chem.*, **27**, 3251 (1962).
(22) M. J. Aroney, C. Y. Chen, R. J. W. LeFèvre, and J. D. Saxby, *J. Chem. Soc.*, 4269 (1964); R. K. Harris and R. A. Spragg, *Chem. Commun.*, 314 (1966).
(23) E. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, p 44.

Using this approach, it has been calculated[24] that approximately 75% of each base is in the equatorial phenyl conformation (IIIA and IVA). This is considered to be a minimum percentage since the calculations did not take into account the effects of bond shortening due to the heteroatoms in the morpholine ring. This would tend to increase the diaxial interactions when compared to similar interactions in cyclohexane.

Since H_a and H_b are *gauche* to each other in both IIIA and IIIB, it might be expected that the value of J_{ab} should be equivalent in either flip conformation. There is, however, reason to believe that this is not the case. It recently has been reported[19,20] that vicinal coupling is dependent on the orientation of electronegative substituents. Consequently, isomeric compounds with similar dihedral angles can show significantly different coupling constants. Accordingly, the diastereomer (VA) having a proton which is *trans* to an electronegative group should show a smaller



VA



VB

vicinal coupling constant than does VB.[19] This phenomenon has also been reported in 2,6-dimethylmorpholine diastereomers[20] where oxygen has a greater effect than nitrogen. For this reason it is expected that conformer IIIA should have a smaller value of J_{ab} than IIIB. Evidence suggesting that this is indeed the case was obtained from the protonated form of III where the average value of J_{ab} was found to be approximately 0.4 cps lower than the corresponding free base. As the spin–spin coupling between the methyl group and the vicinal C-3 proton exhibited no significant difference between the salt and base when examined in the same solvents,[25] this suggested that the difference in J_{ab} was due to an increase in the population of equatorial phenyl conformer (IIIA). Thus, while the free base has been estimated[24] to contain 75% of IIIA, the salt has been calculated[24] to possess this conformer to the extent of approximately 98%. The small decrease in J_{ab} on protonation therefore very likely is due to an increase in the conformer (IIIA) having the lower coupling constant.

Protonation of IV causes an increase in J_{ab}, an effect opposite to that observed with III. The direction of change is not unexpected since the conformational equilibrium would, on protonation, be shifted almost entirely[24] to the equatorial conformer (IVA) at the expense of the axial species (IVB). The change is much larger than that seen when III is compared with its corresponding salt because in this case the difference in the values of J_{ab} for IVA and IVB is much greater. The larger average values of ΔJ_{ab} for the salts, when compared to the bases, also is in accord with the idea that there is a higher population of IIIA and IVA when in the protonated form.

Since III·HCl and IV·HCl are estimated[24] to contain about 98% of conformations IIIA and IVA, respectively, the values of J_{ab} for the salts can be considered to be representative of "pure" 2-axial-3-equatorial and 2,3-diaxial coupling.

The values of J_{ab} for ephedrine (I) and ψ-ephedrine (II) in solvents of widely differing polarity are shown in Table I. The H_aH_b coupling constants of 4.07 and 8.23 cps in $CDCl_3$ solvent agrees very well with the values reported by Hyne.[14] These data suggest that ephedrine resides chiefly in conformations (IA and IB) which possess a *gauche* OH–NHMe relationship, and that IIA is the most populous rotamer in ψ-ephedrine. Among the *gauche* ephedrine rotamers it would be expected that IA should be favored over IB, since the former possesses fewer nonbonded interactions. Purely on the basis of nonbonded interactions the favored ephedrine rotamer should be IC and, if this were the only factor determining the rotameric population, J_{ab} would be much larger than the observed values. The relative insensitivity of J_{ab} to changes in solvent polarity indicates that strong intramolecular hydrogen bonding[12] is, in part, responsible for the above results. The fact that DMSO, a solvent known[26] to form strong hydrogen bonds, produces only a very small change in J_{ab} suggests that ΔG for intramolecular hydrogen bonding compensates for the greater steric interactions present in IA and IB when compared to the less hindered rotamer (IC).

A somewhat different situation exists for ψ-ephedrine in that steric factors enhance rather than oppose intramolecular hydrogen bonding, since rotamer IIA represents the most stable conformation by virtue of possessing fewest nonbonded interactions. On this basis it would be expected that the population of the rotameric species (IIC) that is incapable of internal bonding should be smaller when compared to the corresponding rotamer (IC) in ephedrine. The infrared studies of Kansawa,[12] who reports that the difference in frequency between free and internally bonded OH is greater for ψ-ephedrine, supports this interpretation.

A comparison of ephedrine and ψ-ephedrine with the corresponding morpholines (III and IV) reveals that J_{ab} for ephedrine is approximately 1 cps greater than III, whereas the ψ isomer is smaller than IV by about 0.5 cps. There are two possible reasons for these differences. First, ephedrine and ψ-ephedrine may have small amounts of C rotamers in equilibrium with species A and B. This would tend to increase J_{ab} for ephedrine and produce an opposite effect in ψ-ephedrine. This is supported by the infrared solution spectra[12] of the bases which show a small free OH band. Second, the positions of the conformational equilibria, $A \rightleftharpoons B$, may also contribute to these differences by a mechanism which has been discussed earlier in connection with the morpholines. Hence, J_{ab} for IA should be smaller than for IB, because in the former rotamer H_b is *trans* to the OH group. It would be expected that the A:B ratio in ephedrine would be

(24) The values of $-\Delta G$ (kcal/mole) employed in the calculations were 1.5 for Ph:H and 0.9 for Me:H. In the bases the size of the lone pair of electrons on nitrogen and oxygen was considered to be negligible. This is in accord with the recent observations of N. L. Allinger, J. G. D. Carpenter, and F. M. Karkowski [*J. Am. Chem. Soc.*, **87**, 1232 (1965)] and E. L. Eliel and M. C. Knoeber [*ibid.*, **88**, 5347 (1966)]. For the salts, an additional diaxial interaction was included when required.

(25) The vicinal coupling constants for the methyl group were as follows: in $CDCl_3$, III, 7.1; III·HCl, 7.1; IV, 6.7; IV·HCl, 6.9; in DMSO, I, 6.3, I·HCl, 6.4; II, 6.6; II·HCl, 6.6; III, 6.8; III·HCl, 6.8; IV, 6.2; IV·HCl, 6.3.

(26) O. L. Chapman and R. W. King, *J. Am. Chem. Soc.*, **86**, 1256 (1964).

smaller than in the corresponding model compound III, since the axial protons present in III would be an important factor in the stabilization of conformation IIIA. This would result in a smaller coupling for III. A similar relationship should exist between A and B rotamers of II and IV. In this case, a small difference in the ratio A:B could easily account for the lower H_aH_b coupling of II when compared to IV, since the values of J_{gauche} and J_{trans} differ considerably in magnitude.

There appears to be no profound change in the rotamer distribution of ephedrine and ψ-ephedrine when examined in nonpolar solvents (Table I). This is suggested by the similar values of ΔJ_{ab}. However, in dimethyl sulfoxide (DMSO) a small but significant change in ΔJ_{ab} is observed which is due to an increase and a decrease in the coupling of ephedrine and ψ-ephedrine, respectively. This is consistent with the idea that there is a disruption of a small fraction of intramolecularly bonded rotamers which cause a shift in the conformational equilibria and consequently give rise to higher population of IC.

The coupling constants for salts of ephedrine and ψ-ephedrine (Table II) suggest that the predominant protonated rotamers are identical with those of the free bases (IA and IIA). These rotamers are most probably stabilized by intramolecular hydrogen bonding of the type, ^+N–H·····O. The acidic nature of the bonding proton is undoubtedly an important factor contributing to the stability of such hydrogen bonds. It is significant that the conformation of ephedrine hydrochloride in the crystalline state has been shown[5] to resemble IA. Since this rotamer can be stabilized through internal hydrogen bonding and possesses fewer steric interactions than IB, it is reasonable to expect this species (IA) as the predominant rotamer in solution. This is consistent with the greater basic strength of ψ-ephedrine.[27] The increased basicity of the ψ-isomer over ephedrine has been ascribed to the greater stabilization of the conjugate acid *via* intramolecular ^+N–H·····O bonding.[28]

TABLE II

H_aH_b COUPLING CONSTANTS OF ISOMERIC EPHEDRINE AND RELATED MORPHOLINE SALTS

Solvent	J_{ab} I·HCl	J_{ab} II·HCl	ΔJ_{ab}[a]	J_{ab} III·HCl	J_{ab} IV·HCl	ΔJ_{ab}[b]
$CDCl_3$	...	...	...	2.67	10.36	7.69
TFA[c]	3.74	9.60	5.86	2.56	10.06	7.50
DMSO	2.43[d]	9.42	6.99	2.47	10.02	7.55
D_2O	3.63	9.21	5.58	2.78	10.52	7.74

[a] $II_{J_{ab}} - I_{J_{ab}} = \Delta J_{ab}$. [b] $IV_{J_{ab}} - III_{J_{ab}} = \Delta J_{ab}$. [c] Trifluoroacetic acid. [d] After replacement of exchangeable protons with deuterium. $W_{1/2}$ before exchange was 7.6 cps.

A comparison of the salts of ephedrine and ψ-ephedrine with the corresponding morpholine diastereomers (Table II) in D_2O and trifluoroacetic acid indicates that the values of ΔJ_{ab} for the former isomers are approximately 2 cps smaller than for the morpholines. As was discussed previously in the case of the free bases, this may be related to an increase in the population of the protonated forms of C rotamers at the expense of the internally bonded protonated species (A and B) or possibly to a decrease in the A:B ratio of the rotamer salts.

Of particular significance were the results obtained when the isomeric ephedrinium salts were examined in DMSO. In ephedrine hydrochloride H_a was seen as a multiplet whose width at half-height was 7.6 cps, while the ψ-ephedrine salt showed the expected doublet (J_{ab} = 9.42 cps). When the exchangeable protons in ephedrine hydrochloride were replaced with deuterium, a doublet (J_{ab} = 2.43 cps) emerged in the same position as the multiplet. This suggests that H_a is coupled to both H_b and to the hydroxylic proton (H_O) because H_O is not decoupled by exchange in DMSO.[26] The half-height peak width therefore should be close to $J_{ab} + J_{aO}$. This is in good agreement with the reported[29] spin–spin coupling between hydroxyl and carbinol protons of about 5 cps. With ψ-ephedrine hydrochloride no H_aH_O coupling can be seen because H_O is undergoing more rapid exchange. An explanation for this faster exchange may be related to the greater acidity of H_O in II·HCl as a consequence of stronger internal ^+N–H·····O–H bonding.[27,28]

In view of the strong hydrogen-bonding ability of DMSO, it was rather surprising that J_{ab} in ephedrine hydrochloride is about 1 cps less than values obtained in D_2O and trifluoroacetic acid. In fact, it is very close to III·HCl in the same solvent. This suggests that the protonated form of ephedrine hydrochloride may be in very much the same conformation (IA) as the latter compound (IIIA). A possible explanation for this may be that the bulk of the protonated methylamino group is increased by hydrogen bonding of DMSO with its acidic protons. This would result in an increase in rotamer IA at the expense of IC. It would be expected that the population of IB also would decrease because of the greater interaction imposed by the DMSO-bonded ammonium group. In addition to these factors, it is conceivable that DMSO increases the population of IA by strengthening intramolecular hydrogen bonding. Intermolecular bonding of DMSO with the OH group should result in an increase in the electron density on oxygen and hence endow this atom with enhanced hydrogen-bonding ability. This would result in a lower population of IC.

Examination of ψ-ephedrine hydrochloride in DMSO reveals that J_{ab} is 0.6 cps less than IV·HCl. Employing the same reasoning as in the former case, the observed coupling constant can be ascribed primarily to the weighted average of the salts of IIA and IIB. Since the difference in values of J_{ab} for these rotamers is large[30] the lower coupling constant can be explained on the basis of IIA being the predominant contributor.

Chemical Shifts.—The chemical shift for the benzylic proton (H_a) in the *trans*-morpholine derivative (IV)

(27) V. Prelog and O. Hafliger, *Helv. Chim. Acta*, **33**, 2021 (1950).

(28) J. F. King in "Technique of Organic Chemistry," Vol. XI, Interscience Publishers, Inc., New York, N. Y., 1963, Chapter VI, p 318.

(29) R. J. Ouellette, D. L. Marks, and D. Miller, *J. Am. Chem. Soc.*, **89**, 913 (1967).

(30) An estimate of the percentages of the protonated forms of IIA and IIB in DMSO can be made if it is assumed that the population of IIC is very small and that J_{ab} for I·HCl (2.43 cps) and IV·HCl (10.02 cps) are representative of IIA and IIB, respectively. On this basis a value of 92% of the former and 8% of the latter has been calculated. This represents a maximum percentage for IIB, since J_{ab} for this rotamer is probably less[29] than that of I·HCl.

TABLE III

CHEMICAL SHIFTS[a] OF ISOMERIC EPHEDRINE AND MORPHOLINE BASES

	I		II			III		IV		
Solvent	δ_a	δ_{Me}	δ_a	δ_{Me}	$\Delta\delta_a$[b]	δ_a	δ_{Me}	δ_a	δ_{Me}	$\Delta\delta_a$[c]
CCl_4	...	...	...	...	...	4.66	0.87	3.82	0.73	0.84
C_6H_6	4.67	0.64	4.17	0.71	0.52	4.67	0.90	3.90	0.66	0.77
$CDCl_3$	4.70	0.82	4.16	0.94	0.54	4.80	0.94	4.00	0.80	0.80
DMSO	4.65	0.81	4.27	0.72	0.37	4.63	0.79	3.86	0.70	0.77

[a] Chemical shifts expressed in ppm. [b] $I_{\delta_a} - II_{\delta_a} = \Delta\delta_a$. [c] $III_{\delta_a} - IV_{\delta_a} = \Delta\delta_a$.

TABLE IV

CHEMICAL SHIFTS[a] OF ISOMERIC EPHEDRINE AND MORPHOLINE SALTS

	I·HCl		II·HCl			III·HCl		IV·HCl		
Solvent	δ_a	δ_{Me}	δ_a	δ_{Me}	$\Delta\delta_a$[b]	δ_a	δ_{Me}	δ_a	δ_{Me}	$\Delta\delta_a$[c]
$CDCl_3$	...	...	...	...	...	5.44	1.30	4.81	1.34	0.63
TFA[d]	5.28	1.32	4.86	1.30	0.42	5.15	1.34	4.71	1.26	0.44
DMSO	5.25	0.96	4.64	0.98	0.60	5.04	1.01	4.53	1.04	0.51
D_2O	5.20	1.17	4.77	1.15	0.43	5.38	1.17	4.68	1.15	0.70

[a] Chemical shifts expressed in ppm. [b] $I_{\delta_a} - II_{\delta_a} = \Delta\delta_a$. [c] $III_{\delta_a} - IV_{\delta_a} = \Delta\delta_a$. [d] Trifluoroacetic acid.

is located at approximately 0.8 ppm higher field than the *cis* isomer (III) (Table III). This large difference is most likely related to the orientation of the vicinal methyl group. In the former compound conformations IVA and IVB both have a *gauche* relationship between H_a and the methyl group, whereas in the latter the thermodynamically favored species (IIIA) disposes these groups in an antiparallel manner. Thus, H_a should experience an upfield shift in IV due to shielding by the methyl group.[31] On the other hand, H_a in the favored conformer (IIIA) of the *cis* isomer would be located in the deshielding zone[31] of the methyl group and therefore produce a downfield shift. Taking these opposing effects into consideration, the large difference in chemical shift can be accounted for.

A similar relationship exists for ephedrine and ψ-ephedrine, as it can be observed that the former compound shows the H_a resonance at lower field than does the latter. These data suggest that the preferred rotamers of ephedrine and ψ-ephedrine are similar to those of the corresponding morpholine isomers (IIIA and IVA, respectively).

It is significant that the differences in chemical shifts ($\Delta\delta_a$) between ephedrine and ψ-ephedrine are substantially lower than those found in the morpholines. While it is difficult to draw any firm conclusions concerning the origin of the differences in $\Delta\delta_a$ because the morpholines and ephedrines are probably solvated differently, the consistently lower values of $\Delta\delta_a$ for the latter isomers suggest that rotamers B and C may have contributed to this phenomenon. Accordingly, δ_a for ephedrine would be represented by a weighted average of all staggered conformations, with IA as the preponderant rotamer and minor quantities of IB and IC. Both IB and IC would lower the value of δ_a as a result of the shielding exerted by the *gauche* methyl group. An effect in the opposite direction should occur in ψ-ephedrine due to the deshielding influence of the methyl substituent on H_a in rotamer IIC. It is interesting to note (Table III) that in DMSO solvent the bases (I and II) show a substantially different value for $\Delta\delta_a$ when compared to those obtained in non-polar solvents. This appears to be due to an increased population of IC and IIC due to competition of DMSO for protons involved in intramolecular hydrogen bonding and is in accord with the conclusions which were drawn from the analysis of ΔJ_{ab} values. The fact that the morpholine isomers show only small differences in $\Delta\delta_{ab}$ and ΔJ_{ab} suggests that there is no significant change in the conformational equilibria with different solvents.

The salts of the morpholine and ephedrine isomers (Table IV) showed qualitatively the same type of relationship as the bases with regard to $\Delta\delta_a$. This supports the spin–spin coupling data which suggests that IA and IIA are the chief rotamers. There appears, however, to be no constancy of the $\Delta\delta_a$ values. This may be due in part to the anisotropic effect of polar solvent molecules which could be oriented in such a fashion so as to affect the chemical shift of H_a.

The near magnetic equivalence of the *cis* and *trans* methyl groups in the morpholines is in marked contrast to the corresponding oxazolidines and oxazolidones where it has been reported[32] that the C-methyl group which is *cis* to the aromatic ring can resonate at approximately 0.6 ppm higher field than in the *trans* isomer. The reason for the difference in chemical shift is due to the fact that the greater torsional strain inherent in five-membered rings causes the phenyl and methyl groups in the *cis* isomers to be partially eclipsed with resultant shielding of the methyl group. In the case of the morpholine bases and salts, a substantial difference between the chemical shift of the methyl group in the *cis* and *trans* isomers was observed only when benzene was employed as solvent. The small differences seen in solvents other than benzene are in accord with the *gauche* relationship of the phenyl and methyl groups in the more stable conformations (IIIA and IVA). The difference in δ_{Me} which was seen when benzene was employed is probably related to a difference in solvent orientation[33] with respect to the methyl group in III and IV.

A comparison of the chemical shifts of the C-methyl group in ephedrine and ψ-ephedrine in the same solvents reveals that they have very similar δ_{Me} values.

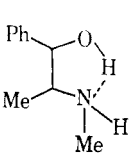
(31) H. Booth, *Tetrahedron*, **22**, 615 (1965).

(32) J. B. Hyne, *J. Am. Chem. Soc.*, **81**, 6058 (1959).

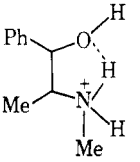
(33) M. J. Aroney, C.-Y. Chen, R. J. W. LeFevre, and A. N. Singh, *J. Chem. Soc.*, 98 (1966).

This provides additional evidence that the preferred conformations (IA and IIA) of these compounds are very similar to those of the more stable morpholine conformers (IIIA and IVA).

Stereostructure–Activity Relationship.—The nmr data strongly suggest that the preferred conformations for ephedrine (I) and ψ-ephedrine (II) bases and salts are IA and IIA, respectively. Further, these rotamers are believed to be stabilized by intramolecular bonds. In the case of the free bases VI, the hydroxyl proton is hydrogen bonded to the basic nitrogen. With the conjugate acids VII, an acidic proton attached to the ammonium group is hydrogen bonded to the oxygen function.



VI



VII

At physiological pH a major fraction of each base is in the ionized form. As it is quite possible that the pharmacological activities of these compounds are dependent on the protonated species, it would be of value to calculate the contribution of various ionized rotamers to the total population in aqueous solution.

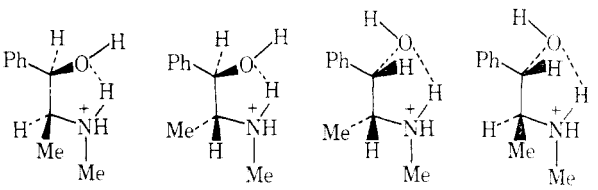
The fraction of *trans*[34] and *gauche* rotamers in ephedrine and ψ-ephedrine salts can be estimated quantitatively from the observed coupling constants (J_{obsd}) if the values of J_{obsd} for III·HCl and IV·HCl are considered to be representative of *gauche* (J_g = 2.8 cps) and *trans* (J_t = 10.5 cps) coupling, respectively. It should be pointed out that this is an approximation, since J_g in ephedrine (IA and IB) and in ψ-ephedrine (IIB and IIC) rotamers probably do not have identical values. This is a consequence[20] of the different orientations of *gauche* protons with respect to the electronegative groups. With the *gauche* rotamers (IA and IB) of ephedrine, this would introduce only a small error since the protons in both the favored rotamer (IA) and the model compound conformation (IIIA) bear the same relationship to the electronegative substituents. Therefore, the calculated percentage of rotamer IC should be slightly higher than the actual value because the population of IB, whose J value is probably between 1 and 2 cps greater[2c] than that of IA, is much lower. In ψ-ephedrine both *gauche* rotamers (IIB and IIC) have their protons arranged differently when compared to IIIA. Rotamer IIB, having both H_a and H_b oriented in an antiparallel fashion with respect to the electronegative groups, should have a coupling constant which is approximately 1 cps less[2c] than that of IIIA. On the other hand, in IIC none of the protons are arranged in this antiparallel orientation and this should result in a value of J_g which is about 2 cps greater[2c] than the model compound III. Since IIB is obviously the main *gauche* contributor, the calculated amount of IIA should therefore be a little less than the real value. The value of J_t derived from the *trans* morpholine (IV·HCl) should be very close to J_t for IC and IIA because an identical relationship of the protons and electronegative groups exists in these conformations.

Employing the J_{ab} values from the model compounds (III·HCl and IV·HCl) in D_2O, the fraction, n, of *trans* rotamer is expressed by

$$n = \frac{J_{obsd} - J_g}{J_t - J_g}$$

Thus, ephedrine hydrochloride (in D_2O) contains approximately 90% *gauche* (IA and IB) and 10% *trans* (IC), while ψ-ephedrine hydrochloride possesses 83–85% *trans* (IIA) and 17–15% *gauche* (IIB and IIC). Since II·HCl forms stronger intramolecular hydrogen bonds than its diastereomer (I·HCl), it appears reasonable that there is much less than 10% of IIC in equilibrium with the rotamers (IIA and IIB) which are capable of internal bonding.

It has been shown[35] that there is a relationship between the direct component of peripherally acting sympathetic amines and absolute stereochemistry at the C-1 center. In general, the (1*R*) configuration favors direct action. It has been pointed out,[35b] however, that this generalization must be viewed with caution if it is applied to compounds containing two asymmetric centers. Hence, of the four ephedrine isomers, only the (1*R*:2*S*) compound possesses some direct activity.[2d,35c] The internally bonded preferred conformations of the protonated ephedrine isomers are depicted below. While no firm conclu-



D-(−) (1*R*:2*S*) | D-(−)-ψ (1*R*:2*R*) | L-(+) (1*S*:2*R*) | L-(+)-ψ (1*S*:2*S*)

sions can be drawn because it is not known whether the preferred ground-state conformation is similar to that found in the drug–receptor complex, it appears significant that D-(−)-ephedrine is the only isomer which possesses both the (1*R*) configuration and a C-methyl group which projects above the plane of the phenethylamine moiety. The D-(−)-ψ isomer also possesses the (1*R*) stereochemistry necessary for direct action, but has the C-methyl group oriented below the plane. It is conceivable that the methyl group in the latter isomer hinders effective interaction with the receptor. In terms of the current adrenergic receptor hypotheses[36,37] this could possibly involve ineffective ion-pair formation.

It is noteworthy that the hydroxyl and methylammonium groups are oriented in a *gauche* fashion. This may signify that ion-pair formation and hydrogen bonding to the receptor *via* the hydroxylic proton occur on the same side of the molecule.

Other sympathomimetic amines containing a benzylic hydroxyl group could possibly be internally

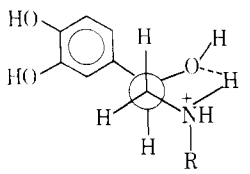
(34) *trans* and *gauche* in this case refer to the orientation of H_a and H_b to each other.

(35) (a) P. N. Patil, A. Tye, and J. B. LaPidus, *J. Pharmacol. Exptl. Therap.*, **149**, 199 (1965); (b) P. N. Patil, J. B. LaPidus, and A. Tye, *ibid.*, **155**, 1 (1967); (c) P. N. Patil, J. B. LaPidus, D. Campbell, and A. Tye, *ibid.*, **155**, 13 (1967).

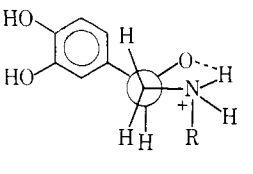
(36) B. Belleau, *Pharmacol. Rev.*, **18**, 131 (1966).

(37) B. M. Bloom and J. M. Goldman, *Advan. Drug Res.*, **3**, 121 (1966).

hydrogen bonded in a manner similar to the ephedrines. For example, epinephrine and norepinephrine might be expected to reside mainly in *gauche* or partially staggered conformations (VIII and IX, respectively). While the nonbonded interactions are



VIII



IX

minimized in VIII, the latter rotamer (IX) is also a possibility since the internal hydrogen bond in IX would be stronger due to the shorter distance between the donor proton and acceptor group. This could compensate for the greater steric interaction due to partial staggering. No significant partial eclipsing was observed in the ephedrines because of the severe interaction which would be created between the phenyl and methyl groups. Internal bonding may not only stabilize these amines in a conformation favorable to amine–receptor association, but also would render the hydroxylic proton more acidic and consequently promote stronger hydrogen bonding with the receptor.

The ephedrine isomers are known[2e] to show only very minor differences in central stimulant activity. It recently has been reported[38] that there is little, if any, direct action associated with these compounds. The fact that pipradrol possesses stereospecificity[39] and a high degree of direct action has led to the generalization[40] that the receptors involved in direct central action possess greater steric demands than do the sites associated with the release of endogenous catecholamines. Consequently, the conformational requirements for the indirect action of these compounds in the CNS may not be very critical.

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

Experimental Section

All spectra were obtained with a Varian A-60 nuclear magnetic resonance spectrometer at an operating frequency of 60 Mc/sec. Chemical shifts are considered accurate to ±0.02 ppm and the spin–spin coupling constants were within ±0.1 cps of the mean values reported. Each sample was run as a 10% (w/v) solution. The probe temperature was 37 ± 1°.

Ephedrine was obtained from a commercial source (Merck) as were ψ-ephedrine (Burroughs Wellcome) and *trans*-3-methyl-2-phenylmorpholine (Geigy). *cis*-3-Methyl-2-phenylmorpholine was prepared according to the method of Clarke.[21]

Acknowledgment.—The author is indebted to Mr. Kenneth Stenglein for preparing *cis*-3-methyl-2-phenylmorpholine and to Dr. Norbert Gruenfeld of Geigy Research Laboratories for supplying the *trans* isomer. This work was supported by Public Health Service Grant GM 09402 from the National Institute of General Medical Sciences.

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

(40) P. S. Portoghese, T. L. Pazdernik, W. L. Kuhn, G. Hite, and A. Shafi'ee, *J. Med. Chem.*, in press.

Reaction of Cyclic β-Diketones with 3,4-Dihydroisoquinolines and Related Compounds. Preparation and Anticancer Activity of 2-Substituted 1,3-Cyclohexanediones

MAX VON STRANDTMANN, MARVIN P. COHEN, AND JOHN SHAVEL, JR.

Department of Organic Chemistry, Warner-Lambert Research Institute, Morris Plains, New Jersey

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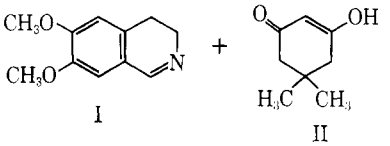
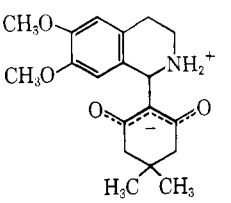
1,3-Cyclohexanediones add readily to 3,4-dihydroisoquinolines, 3,4-dihydro-β-carbolines, and quinazoline. Some of the resulting 2-substituted 1,3-cyclohexanediones are active in experimental tumor systems.

Recently, we have described a synthesis of benzo[*a*]-quinolizines[1] by the reaction of linear β-diketones with 3,4-dihydroisoquinolines. The present communication concerns the reaction of cyclic β-diketones with 3,4-dihydroisoquinolines and other partially reduced heterocyclic nuclei having an activated C=N function.[2] The reaction is characterized by rapid rate and high yields. For example, addition of 6,7-dimethoxy-3,4-dihydroisoquinoline (I) to dimedone (II) produced



I II



III

within seconds a crystalline precipitate of III in 95% yield. Compounds prepared by this method are summarized in Table I.

(1) M. von Strandtmann, M. P. Cohen, and J. Shavel, Jr., *J. Org. Chem.*, **31**, 797 (1966).

(2) Related reactions of corresponding carbinolamines such as cotarnine (1-hydroxy-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline) and hydrastine (1-hydroxy-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline) with compounds having activated methylene groups have been described by C. Liebermann and K. Kropf, *Ber.*, **37**, 211 (1904).