cedure F).—A solution of VIII (2.6 g., 0.012 mole) and hydroxylamine (1.65 g., 0.050 mole) in 50 ml. of methanol was refluxed with stirring for 4 days. The solution was evaporated and the residue was extracted with ten 100-ml. portions of ether. The ether solution was evaporated to 15 ml. and chromatographed on an acid-washed alumina column. Elution with 1:1 hexane–ether gave crude product which was vacuum sublimed (60° and 0.2 mm.) to give colorless crystals of 1-hydroxylamino-3-methyliminopentafluorocyclopentene (XXIII), 1.4 g. (54%), m.p. 108.0–108.5°.

Further elution gave no trioxime XIX.

More Vigorous Conditions.—Using procedure F, VIII (10.8 g., 0.050 mole) and hydroxylamine (36.3 g., 1.1 moles) in 820 ml. of methanol, after 7 days at reflux, gave colorless crystals of 1-hydroxylamino-3-methyliminopentafluorocyclopentene (XXIII), 6.6 g. (62%), m.p. 95–107°. Recrystallization from chloroform and vacuum sublimation (55° and 0.2 mm.) failed to change the melting point.

Further elution gave no trioxime XIX.

Reaction of 1-Methylamino-2-chloro-3-methyliminotetrafluorocyclopentene (IX) with Hydroxylamine. Mild Conditions.—Using procedure F, IX (2.0 g., 0.0083 mole) and hydroxylamine (1.65 g., 0.050 mole) in 50 ml. of methanol, after 4 days at reflux, gave colorless crystals of 1-hydroxylamino-2-chloro-3-methyliminotetrafluorocyclopentene (XXIV), 1.0 g. (50%), m.p. 147–149°.

Further elution gave no trioxime XIX.

More Vigorous Conditions.—Using procedure F, IX (11.5 g., 0.050 mole) and hydroxylamine (36.3 g., 1.1 moles) in 820 ml. of methanol, after 7 days at reflux, gave colorless crystals of 1-hydroxylamino-2-chloro-3-methyliminotetrafluorocyclopentene (XXIV), 4.0 g. (35%), m.p. 140–148°.

Further elution gave 1,2,3-trioximinotetrafluorocyclopentane (XIX) as a cream solid, 0.50 g. (4.4%), m.p. 164° dec.

Acknowledgment.—We wish to thank Hooker Chemical Corporation for financial support of this work and a fellowship of J. J. T.

Stereoisomeric Enamines. I. Preparation and Characterization[1a,b]

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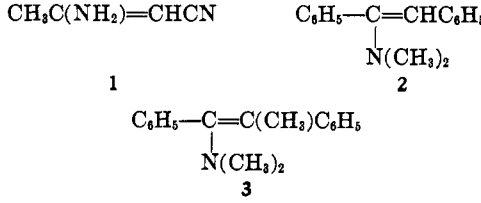
A new approach to the synthesis of stereoisomeric enamines of known configuration is described which takes advantage of the well-documented facility and stereospecificity of the bimolecular β elimination reaction. Treatment of the mesitoate esters of *dl-threo-* and *dl-erythro*-1-(4-morpholino)-1,2-diphenylethanol (**6b** and **8b**, respectively) with potassium *t*-butoxide in dimethyl sulfoxide gave rise to *trans-* and *cis*-1-(4-morpholino)-1,2-diphenylethylene, respectively. Assignment of configuration, relative stability of stereoisomers, and their n.m.r. spectra are discussed.

The general procedures for the preparation of enamines,[2,3] while providing broad scope, fail to incorporate the desirable feature of stereospecificity. The present availability of synthetic methods cannot be considered adequate without the addition of one or more which are stereospecific in character. It is the object of this communication to describe one approach to the fulfillment of this need.

The recorded reports of the synthesis of enamines which can exist as geometric isomers are generally characterized by the absence of a discussion of the stereochemical constitution of the products. It is likely that, where possible, mixtures of stereoisomers are obtained when employing the general procedures[2] whose composition is the result of thermodynamic control. That this is undoubtedly so in the presence of an acid catalyst will be illustrated later. In those cases where the isolation of a single stereoisomer is reported, the synthesis can not be described as stereospecific and the assignment of configuration, if specified, can not be considered rigorous.

The reaction of acetonitrile with sodium is reported[4] to yield either *cis-* or *trans*-β-aminocrotonitrile (**1**), depending on work-up. Assignment of configuration is based on melting point and solubility. Although the authors rule out polymorphic modifications on the basis of thermochemical behavior, it should be noted that the ultraviolet spectra are nearly identical: *cis*, $\lambda_{max}^{acetonitrile}$ 254.5 mμ (ϵ 12,430); *trans*, $\lambda_{max}^{acetonitrile}$ 254.5 mμ (ϵ 13,650).

The *trans* configuration is suggested for enamine **2**, formed in the base-induced dehydrocyanation of 1-(N,N-dimethylamino)-1-cyano-1,2-diphenylethane.[5] Based on the results reported in this paper, that assignment of configuration is suspect. In a similar reaction 1-(N,N-dimethylamino)-1-cyano-2-methyl-1,2-diphenylethane is reported to give rise to a separable mixture of stereoisomeric enamines (**3**); however, assignment of configuration is absent. The authors are careful to point out that a satisfactory elemental analysis was obtained for only one of the two "stereoisomers."



In a study of the preparation of a series of aldehyde enamines (**4**) by the method of Mannich,[2a] Dulou, Elkik, and Veillard[6] assigned the *trans* configuration to the predominant stereoisomer, in what appeared to be

(1) (a) Support of this project by a research grant from Parke, Davis and Co. is gratefully acknowledged. (b) Presented in part before the Division of Organic Chemistry at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1964. (c) Parke, Davis Research Fellow 1962–1964.

(2) The two most widely employed procedures are (a) condensation of an aldehyde with a secondary amine in the presence of potassium carbonate [C. Mannich and H. Davidsen, *Ber.*, **69**, 2106 (1936)]; (b) azeotropic removal of water from a solution of a ketone and secondary amine in benzene, frequently in the presence of an acid catalyst. [F. E. Heyl and M. E. Herr, *J. Am. Chem. Soc.*, **75**, 1918 (1953)].

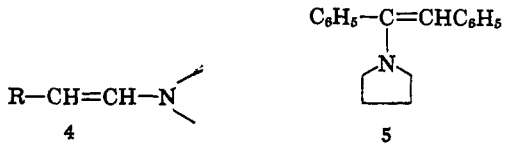
(3) For a brief review of methods of synthesis, see the chapter on enamines, J. Szmuszkovicz, *Advan. Org. Chem.*, **4**, 1 (1963).

(4) J. J. Conn and A. Taurins, *Can. J. Chem.*, **31**, 1211 (1953).

(5) C. R. Hauser, H. M. Taylor, and T. G. Ledford, *J. Am. Chem. Soc.*, **82**, 1786 (1960).

(6) R. Dulou, E. Elkik, and A. Veillard, *Bull. soc. chim. France*, 967 (1960).

mixtures of stereoisomers, on the basis of infrared and ultraviolet spectral properties. The stereochemical compositions of the enamine mixtures were not reported. The removal of water from a mixture of



desoxybenzoin and pyrrolidine gave rise to a sharp-melting (40–42°) enamine (**5**) to which the *trans* configuration was assigned based on a comparison of its ultraviolet spectrum [λ_{max} 227 mμ (ε 12,500) and 312 mμ (ε 18,900)] with that of *trans*-stilbene and triphenylethylene. This assignment of stereochemistry must also be questioned in light of the results presented in this paper.

A consideration of the design of a stereospecific synthesis of enamines suggested that at least two requirements must be met. First, if the introduction of the double bond was to be the final step, it must be stereospecific in character, and, second, the enamine, once formed, must retain its stereochemical integrity under the conditions employed in the double-bond-forming step. The base-induced bimolecular β elimination reaction fulfills both of these requirements. The *trans* nature of the E2 elimination in acyclic systems is abundantly documented[7] and, in addition, the facile isomerization of the double bond that would be anticipated in any procedure employing acidic conditions (*vide infra*) is circumvented. This approach resulted in the synthesis of a pair of stereoisomeric enamines—*trans*- and *cis*-1-(4-morpholino)-1,2-diphenylethylene (**7** and **9**), respectively—of *anticipated configuration*, the first such documented report.

The reaction of *cis*- and *trans*-stilbene oxide with morpholine in the presence of morpholine hydrobromide provided the required, chromatographically pure, starting materials, *dl-threo*-2-(4-morpholino)-1,2-diphenylethanol (**6a**) and *dl-erythro*-2-(4-morpholino)-1,2-diphenylethanol (**8a**), in yields of 65 and 85%, respectively. An identical stereochemical course was observed in both cases in the absence of morpholine hydrobromide,[8] thus eliminating the possibility of an acid-catalyzed *cis* opening of the epoxide and permitting the assignment of configuration of the β-amino alcohols on the basis of the anticipated cleavage of the epoxide ring with inversion of configuration.[9] The diastereomeric β-amino alcohols **6a** and **8a** were converted to the corresponding mesitoate esters, **6b** and **8b**, respectively, upon treatment with mesitoyl chloride, conditions expected to maintain the stereochemical integrity of the molecules. This latter point was conclusively established by the observation that the lithium aluminum hydride reduction of mesitoate esters **6b** and **8b** gave rise to the chromatographically pure β-amino alcohols **6a** and **8a**, respectively.

(7) J. F. Bunnett, *Angew. Chem., Intern. Ed. Engl.*, **1**, 225 (1962).

(8) A similar result was observed by C. L. Browne and R. E. Lutz [*J. Org. Chem.*, **17**, 1187 (1952)] in a study of the reaction of the stilbene oxides with piperidine.

(9) See chapter on ethylene and trimethylene oxides by S. Winstein and R. B. Henderson, "Heterocyclic Compounds," Vol. I, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1950.

The required β elimination of the elements of mesitoic acid from the *dl-threo* ester **6b** was successfully effected by treatment with 1.5 *M* potassium *t*-butoxide in dimethyl sulfoxide. A quantitative yield of crude *trans*-enamine **7** was obtained, from which a 65% yield of pure *trans*-enamine could be isolated. The enamine structure is consistent with elemental analysis, the product of acid hydrolysis, and infrared, ultraviolet, and n.m.r. spectral properties (Table I). Configuration is assigned of the basis of the anticipated *trans* nature of the elimination reaction[7] and the results of hydration of the double bond *via* hydroboration described below.

TABLE I

SPECTRAL PROPERTIES

	Infrared[a] ($\nu_{C=C}$), cm.$^{-1}$	Ultraviolet,[a] λ_{max}, mμ (ε)	N.m.r.[a,b] (vinyl proton signal), δ (p.p.m.)
cis-Enamine	1617	306 (11,600) 224 (14,800)	5.56[c]
trans-Enamine	1611	320 (11,400) 240 (14,600)	5.71[c]

[a] Run in cyclohexane. [b] Tetramethylsilane is used as an internal standard. [c] A sharp singlet whose integrated intensity corresponds to a single proton.

Similar treatment of the *dl-erythro* ester **8b** gave rise to a 57% yield of the pure *cis*-enamine **9**. Assignment of the *cis*-enamine structure is compatible with its spectral properties (Table I) and the results of acid hydrolysis and hydration *via* hydroboration (*vide infra*).

With regard to the n.m.r. data in Table I, it is interesting to note that chemical shifts of $\delta = 6.38$ and 6.64 p.p.m., respectively, have been reported[10] for the vinyl proton signals of *cis*- and *trans*-1-*n*-butyl-1,2-diphenylethylene. Thus the observation made by Stork[11] that an electron donor at the site of unsaturation shifts the vinyl proton signal to higher field appears to hold in this case. Also of interest is the observation that the vinyl proton signals of both *trans*-1-*n*-butyl-1,2-diphenylethylene and the *trans*-enamine **7** appear at lower field than the corresponding *cis* isomers.

The readily observed difference in chemical shift between the vinyl proton signals of the *cis*- and *trans*-enamine suggested a convenient device by which the degree of stereospecificity of the elimination step could be determined. Examination of the n.m.r. spectrum of the crude enamine arising from the *dl-threo* mesitoate ester **6b** revealed the complete absence of a signal corresponding to the vinyl proton of the *cis*-enamine **9**. The configurational homogeneity of the product suggests a *high degree of stereospecificity in the elimination step* in view of the observation that the *trans*-enamine is the thermodynamically least stable stereoisomer (*vide infra*).

To our surprise the crude enamine arising from the *dl-erythro* mesitoate ester **8b** proved to be a mixture containing approximately 75% of the expected *cis*-enamine **9** and 25% of the unexpected *trans*-enamine **7**. It was clearly demonstrated that these results are *not* explicable in terms of the instability of the *cis*-enamine under the reaction conditions employed. Indeed, it

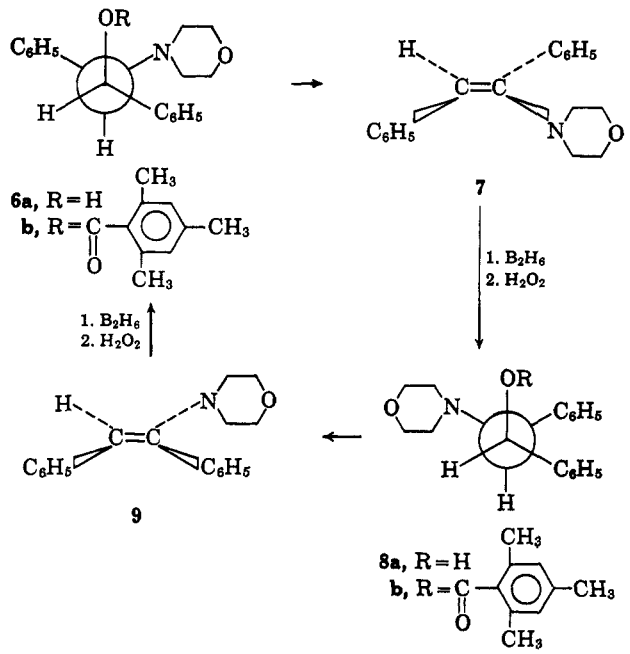
(10) J. E. Mulvaney, Z. G. Garlund, and S. L. Garlund, *J. Am. Chem. Soc.*, **85**, 3895 (1963).

(11) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *ibid.*, **85**, 207 (1963).

could be shown that *both* stereoisomeric enamines retain their configurational integrity over long periods of time under these conditions.

It its present modification,[12] the method leads to the *trans*-enamine with a high degree of stereospecificity, ostensibly *via* a mechanism possessing E2 character. However, the course of the elimination step leading to the preparation of the *cis*-enamine appears to be questionable at the present time, albeit the product of anticipated configuration (and greatest thermodynamic stability) is obtained in good yield.[13] The fact that the elimination in the case of the *dl-erythro* mesitoate ester **8b** is indeed base induced was demonstrated by its stability in dimethyl sulfoxide in the absence of potassium *t*-butoxide.

The anti-Markovnikov, *cis* hydration of the carbon–carbon double bond *via* hydroboration[14,15] appeared to present an attractive means for the confirmation of the configurational assignments in view of the availability



of the anticipated products, the diastereomeric amino alcohols **6a** and **8a**. A gas chromatographic analysis of the crude basic product arising from hydration of the *cis*-enamine **9** revealed the presence of a 32% yield of the *dl-threo* amino alcohol **6a**, the anticipated product of *cis* hydration, and *none* of the corresponding *dl-erythro* amino alcohol **8a**. A second component, identified as 1-(4-morpholino)-1,2-diphenylethane by comparison with an authentic sample prepared by catalytic reduction of the *cis*-enamine **9**, was detected in 28% yield. The latter product is considered to arise by the alkali-catalyzed dealkylation of the benzylic organoborane intermediate during the oxidation step.[16]

The results of hydration of the *trans*-enamine **7**, while not so convincing, still support the assignment of configuration. Under identical conditions with those employed in the hydration of the *cis*-enamine, the *trans*-enamine **7** gave rise to both the expected *dl-erythro* amino alcohol **8a** and the unexpected *dl-threo* amino alcohol **6a** in the approximate ratio of 3:2 (total yield of amino alcohol was 33%). In addition, the product of dealkylation of the intermediate organoborane, 1-(4-morpholino)-1,2-diphenylethane, was detected in 26% yield. Since the stability of the *dl-erythro* amino alcohol **8a** under conditions of its formation and analysis has been demonstrated, it is suggested that the *dl-threo* amino alcohol **6a** arises as a result of partial isomerization of the *trans*-enamine **7** to the *cis* isomer *prior* to hydroboration under the influence of either boron trifluoride or diborane.

The results of hydration *via* hydroboration are indicative of the greater stability of the *cis*-enamine as compared with that of the *trans* isomer. In this connection it may be noted that Cristol and Pappas[17] report that *cis*-1-*p*-toluenesulfonyl-1,2-diphenylethylene is more stable than the corresponding *trans* isomer. The steric factor suggested by these authors to account for their observation may not be operative in the enamine case since the steric requirement of the morpholino group is undoubtedly less than that of a *p*-toluenesulfonyl group.

The tendency of the *trans*-enamine to isomerize to the *cis*-enamine was readily observed in the laboratory on numerous—sometimes inconvenient—occasions under unexpectedly mild conditions and necessitated not only great care in handling, but the establishment of configurational homogeneity just prior to use by analysis of the ultraviolet or n.m.r. spectrum. Similar difficulties in handling were not encountered with the *cis*-enamine.

In a more quantitative study, approximate initial first-order rate constants for the isomerization of *trans*-enamine **7** to the *cis*-enamine **9** were determined in methanol solution in the absence and the presence of added acid and base. The kinetics were followed only for the first 25–35% of isomerization in order to avoid errors arising from the competitive isomerization of the *cis*-enamine to the *trans* isomer. The unimolecular nature of the isomerization is more assumed than established, since, although the linearity of a plot of the logarithm of the concentration of the *trans*-enamine *vs.* time was demonstrated for that portion of the reaction followed, the isomerization was not followed to the extent necessary to rule out higher order reactions on the basis of the nonlinearity of the experimentally derived curves.

The results of the study are summarized in Table II. The significant rate of isomerization of the *trans*-enamine in pure methanol at room temperature was surprising, although the rate enhancement observed in the presence of even small amounts of boron trifluoride is to be expected[18] and suggests the intervention of

(12) The role of base, solvent, and leaving group are receiving attention. Attempts to eliminate the elements of mesitoic acid in a 1 *M* solution of potassium *t*-butoxide in *t*-butyl alcohol at reflux temperatures led only to recovered ester.

(13) The mechanistic implications of the results of the elimination reaction are presently under more detailed investigation. It is possible that while the *dl-threo* mesitoate ester **6b** yields the *trans*-enamine **7** *via* an E2 elimination, the products arising from the corresponding *dl-erythro* ester **8b** may be the result of a reaction proceeding *via* a carbanionic intermediate. Such a set of circumstances could require $k_{E2}(threo) > k$(carbanion formation) $> k_{E2}(erythro)$.

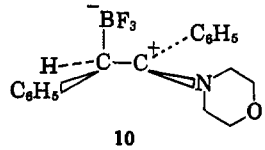
(14) G. Zweifel and H. C. Brown, *Org. Reactions*, **13**, 1 (1963).

(15) We are grateful to Professor A. J. Weinheimer of the University of Oklahoma for the disclosure, prior to publication, of his results on the hydration of enamines in this manner.

(16) A. J. Weinheimer and W. E. Marsico, *J. Org. Chem.*, **27**, 1926 (1962).

(17) S. J. Cristol and P. Pappas, *ibid.*, **28**, 2066 (1963).

(18) Boron trifluoride has been reported to isomerize *cis*-stilbene to *trans*-stilbene: C. C. Price and M. Meister, *J. Am. Chem. Soc.*, **61**, 1595 (1939).



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complex **10**. The addition of sodium methoxide appears to result in a retardation of the rate of isomerization. The composition of the equilibrium mixture shown in Table II clearly reflects the greater stability

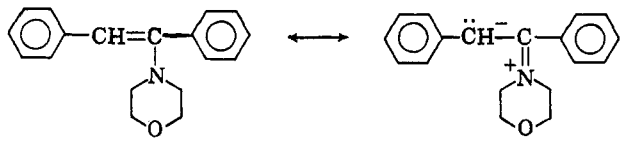
TABLE II

ISOMERIZATION OF THE *trans*-ENAMINE **7** AT 25°

System	$k_1 \times 10^3$ min.$^{-1}$	Half-life, min.	Equilibrium composition
1. CH_3OH	1.3 ± 0.05	542 ± 21	$88 \pm 2\%$ *cis*[a]
2. CH_3OH—BF_3[b]	12 ± 0.2	59 ± 1	$12 \pm 2\%$ *trans*
3. 2.5% $NaOCH_3$ in CH_3OH	0.68 ± 0.06	1030 ± 90	

[a] The same equilibrium composition was obtained starting with the more stable *cis*-enamine. [b] The methanol solution was approximately 3.5×10^{-7} *M* in boron trifluoride etherate.

of the *cis*-enamine, while the facile isomerization observed for the *trans*-enamine, *e.g.*, compared with the known stability of *cis*-stilbene and its α-alkyl derivatives, may indicate that the introduction of an electron-donating amino group at the site of unsaturation lowers the energy barrier to rotation. In resonance terms, the data suggest an increased contribution by the polar resonance forms as **11**.



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The greater stability of the *cis*-enamine **9** was also observed in the direct preparation of the enamine from the acid-catalyzed condensation of desoxybenzoin and morpholine, conditions which would be expected to give rise to the product of thermodynamic control. A 75% yield of the pure *cis*-enamine **9**, m.p. 90–92°, was isolated; however, fractional crystallization techniques yielded no *trans*-enamine **7**. A similar preparation has been reported by Takeuchi and Nomura[19] to yield 1-(4-morpholino)-1,2-diphenylethylene, m.p. 86–88° (methanol). No assignment of configuration is offered by these authors.

Experimental Section[20]

***cis*-Stilbene Oxide.**—A solution of 15.0 g. (0.083 mole) of *cis*-stilbene and 15.5 g. (0.090 mole) of *m*-chloroperbenzoic acid[21] in 150 ml. of chloroform was refluxed for 12 hr. The resulting mixture was cooled and filtered. The filtrate was washed thoroughly with a saturated sodium bicarbonate solution and then with water. The organic layer was separated, dried over anhydrous calcium sulfate, and evaporated *in vacuo* to yield an oily product which was crystallized from ethanol to yield 9.1 g. (56%) of crude solid material, m.p. 36–38°. Recrystallization gave 6.9 g. (42%) of a white crystalline solid, m.p. 38–39° (lit.[22] m.p. 37.0–37.5°).

***trans*-Stilbene Oxide.**—Following the procedure described above for the preparation of *cis*-stilbene oxide, *trans*-stilbene oxide was obtained in 74% yield, m.p. 65.5–67.0° (methanol, lit.[22] m.p. 69.0–69.5°).

***dl-threo*-2-(4-Morpholino)-1,2-diphenylethanol (6a). Method A.**—A mixture of 1.5 g. (0.0077 mole) of *cis*-stilbene oxide, 1.0 g. (0.012 mole) of morpholine, and 0.5 g. (0.0030 mole) of morpholine hydrobromide was immersed in an oil bath (90–95°). After 72 hr. the reaction mixture was taken up in absolute ether and acidified with ethereal hydrochloric acid. The mixture of hydrochlorides was collected by filtration and dissolved in water. The product was precipitated by the addition of sodium hydroxide to yield 1.9 g. (88%) of crude solid, m.p. 140–145°. Recrystallization from ethanol yielded 1.4 g. (65%) of an analytically pure white crystalline solid, m.p. 150–151°.

Gas chromatographic analysis of the crude solid showed the absence of the isomeric *dl-erythro*-2-(4-morpholino)-1,2-diphenylethanol (**8a**). This method was shown to detect the presence of less than 5% of **8a**.

Anal. Calcd. for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.95. Found: C, 76.03; H, 7.51; N, 4.79.

The hydrochloride salt of the alcohol **6a** was prepared in quantitative yield by treating the alcohol **6a** with a saturated solution of hydrogen chloride in ether, m.p. 229–230.5° (ethanol).

Anal. Calcd. for $C_{18}H_{22}ClNO_2$: C, 67.59; H, 6.94; N, 4.38. Found: C, 67.40; H, 7.02; N, 4.21.

Method B.—A solution of 4.7 g. (0.024 mole) of *cis*-stilbene oxide in 3.9 g. (0.045 mole) of morpholine was refluxed for 24 hr. The resulting reaction mixture was poured into 50 ml. of water and the solid that separated was collected by filtration and dried *in vacuo* to yield 6.5 g. (95%) of crude solid material, m.p. 144–147°. Recrystallization from ethanol gave 5.2 g. (76%) of an analytically pure white crystalline solid, m.p. 150–151°.

A mixture melting point with the alcohol derived from procedure A above gave no depression. The infrared absorption spectra of the alcohols from both sources are identical in every detail.

***dl-erythro*-2-(4-Morpholino)-1,2-diphenylethanol (8a). Method A.**—Following procedure A outlined above for the preparation of *dl-threo*-2-(4-morpholino)-1,2-diphenylethanol (**6a**), 11.0 g. (0.056 mole) of *trans*-stilbene oxide produced 11.4 g. (96%) of crude solid, m.p. 117–119°, and 10.1 g. (85%) of a pure white crystalline solid, m.p. 125–126.5° (ethanol).

Vapor phase chromatographic analysis of the crude solid product revealed the absence of the isomeric *dl-threo*-2-(4-morpholino)-1,2-diphenylethanol (**6a**).

Anal. Calcd. for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.95. Found: C, 76.02; H, 7.73; N, 4.85.

The hydrochloride salt of the alcohol **8a** crystallized from ethanol, m.p. 258–259.5° (lit.[23] m.p. 155–157°).

Anal. Calcd. for $C_{18}H_{22}ClNO_2$: C, 67.59; H, 6.94; N, 4.38. Found: C, 67.31; H, 6.99; N, 4.24.

Method B.—Following procedure B outlined above for the preparation of *dl-threo*-2-(4-morpholino)-1,2-diphenylethanol (**6a**) 10.0 g. (0.051 mole) of *trans*-stilbene oxide produced 13.4 g. (93%) of crude solid, m.p. 116–119°, and 10.8 g. (75%) of an analytically pure white crystalline solid, m.p. 125–126.5° (methanol).

A mixture melting point with the alcohol from the procedure A above gave no depression. The infrared absorption spectra of the alcohols from both sources are identical in every detail.

***dl-threo*-2-(4-Morpholino)-1,2-diphenylethyl Mesitoate (6b).**—A mixture of 3.9 g. (0.014 mole) of the amino alcohol **6a** and 7.6 g. (0.042 mole) of mesitoyl chloride was heated at 90–95° for 7 hr. The resulting solid mass was crushed into a flask containing 150 ml. of 10% sodium hydroxide solution and 300 ml. of ether, and the mixture was stirred magnetically until all the solid dissolved. The ether layer was separated, washed with water,

(19) Y. Takeuchi and Y. Nomura, *Sci. Papers Coll. Gen. Educ., Univ. Tokyo*, **11**, 193 (1961); *Chem. Abstr.*, **58**, 4550 (1963).

(20) All melting points were taken on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Infrared absorption spectra were determined as potassium bromide pellets on a Perkin-Elmer Model 137 or 237B Infracord. The ultraviolet absorption spectra were determined on a Cary Model 14 recording spectrophotometer using quartz cells. N.m.r. spectra were run in an appropriate solvent on a Varian Associates A-60 spectrometer with tetramethylsilane as an internal standard. Chemical shift is reported in δ values (parts per million). Gas chromatographic analyses were obtained on 6-ft. glass column using a thermal conductivity detection system and helium as the carrier gas. The packing used was 2% XE-60 on Anakrom ABS. In all cases a column temperature of 230° and gas pressure of 15 p.s.i. were used. Microanalyses were determined by Midwest-Microlab, Inc., Indianapolis, Ind.

(21) Supplied by FMC Corp., New York, N. Y.

(22) D. Y. Curtin and D. B. Kellom, *J. Am. Chem. Soc.*, **75**, 6011 (1953).

(23) R. E. Lutz, J. A. Freek, and R. S. Murphy, *ibid.*, **70**, 2015 (1948).

and dried over anhydrous calcium sulfate. Crystallization from ethanol of the product obtained after removal of ether yielded 2.9 g. (49%) of crude solid, m.p. 152–155°. Recrystallization yielded 2.5 g. (42%) of an analytically pure crystalline solid, m.p. 160–161.5°.

Anal. Calcd. for $C_{28}H_{31}NO_3$: C, 78.29; H, 7.28; O, 11.17. Found: C, 78.21; H, 7.56; O, 11.19.

***dl-erythro*-2-(4-Morpholino)-1,2-diphenylethyl Mesitoate (8b).**—Following the procedure outlined above for the preparation of *dl-threo*-2-(4-morpholino)-1,2-diphenylethyl mesitoate (**6b**), the amino alcohol **8a** (1.5 g., 0.0053 mole) produced 0.89 g. (39%) of crude solid, m.p. 190–193°, and 0.72 g. (32%) of an analytically pure crystalline solid, m.p. 193–194.5° (ethanol).

Anal. Calcd. for $C_{28}H_{31}NO_3$: C, 78.29; H, 7.28; O, 11.17. Found: C, 78.22; H, 7.32; O, 11.30.

Lithium Aluminum Hydride Reduction of *dl-erythro*-2-(4-Morpholino)-1,2-diphenylethyl Mesitoate.—Reduction of 100 mg. (0.233×10^{-3} mole) of *dl-erythro*-2-(4-morpholino)-1,2-diphenylethyl mesitoate with 12 mg. (0.315×10^{-3} mole) of lithium aluminum hydride was effected by refluxing in 10 ml. of ether under an atmosphere of nitrogen for 30 min. Water was cautiously added to the reaction mixture; the reaction mixture was made acidic with 25% hydrochloric acid and extracted with ether to remove nonbasic components. The acidic aqueous solution was then made basic with 10% sodium bicarbonate solution and extracted with ether. Evaporation of the dried basic ethereal extract yielded a white solid, 45 mg. (68%), m.p. 123–125°. A gas chromatographic analysis revealed the presence of *dl-erythro*-2-(4-morpholino)-1,2-diphenylethanol and none of the corresponding *dl-threo* isomer.

A mixture melting point with authentic *dl-erythro*-2-(4-morpholino)-1,2-diphenylethanol gave no depression. The infrared absorption spectrum was identical in every detail with an authentic sample.

Lithium Aluminum Hydride Reduction of *dl-threo*-2-(4-Morpholino)-1,2-diphenylethyl Mesitoate.—Following the procedure outlined above for the reduction of *dl-erythro*-2-(4-morpholino)-1,2-diphenylethyl mesitoate, the *dl-threo* ester (100 mg., 0.233×10^{-3} mole) yielded a white solid, 45 mg. (68%), m.p. 148–150°. A gas chromatographic analysis revealed the presence of *dl-threo*-2-(4-morpholino)-1,2-diphenylethanol and none of the corresponding *dl-erythro* isomer.

A mixture melting point with authentic *dl-threo*-2-(4-morpholino)1,2-diphenylethanol gave no depression. The infrared absorption spectrum was identical in every detail with that of an authentic sample.

Preparation of Potassium *t*-Butoxide Solutions.—Potassium *t*-butoxide[24] was purified by sublimation under 0.1-mm. pressure at 155–160° and transferred to a brown bottle in a dry nitrogen atmosphere. The bottle was sealed with a serum cap, and the appropriate amount of purified, anhydrous dimethyl sulfoxide was added into the bottle with a syringe. The necessary amount of solution was removed by syringe just prior to using.

***cis*-1-(4-Morpholino)-1,2-diphenylethylene (9).**—All glassware employed was base washed and dried thoroughly. To 15 ml. of 1.5 *M* potassium *t*-butoxide in dimethyl sulfoxide was added 0.40 g. (0.00093 mole) of the *dl-erythro* mesitoate ester **8b**. After stirring for 3 hr. at room temperature under a nitrogen atmosphere the mixture was poured into 75 ml. of ice-cold water. The cloudy solution was extracted three times with 25-ml. portions of ether, and the organic layer was dried quickly over anhydrous potassium carbonate. Evaporation of the dried ether extract *in vacuo* yielded 0.23 g. (93%) of crude oily enamine. Crystallization from methanol gave 0.14 g. (57%) of analytically pure, crystalline *cis*-enamine, m.p. 90–92°, $\lambda_{max}^{cyclohexane}$ 306 mμ (ε 11,600) and 224 mμ (ε 14,800).

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.57; H, 7.35; N, 5.49.

Catalytic hydrogenation of the enamine in ethyl acetate over a platinum oxide catalyst at room temperature and atmospheric pressure gave 1-(4-morpholino)-1,2-diphenylethane in 90% yield, m.p. 64–65° (50% aqueous ethanol).

Anal. Calcd. for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 81.09; H, 8.04; N, 5.22.

The vinyl proton signal in the n.m.r. spectrum (cyclohexane) of the analytically pure sample of *cis*-enamine appears as a sharp singlet (integrated intensity corresponding to one proton) at δ = 5.56 p.p.m. The aromatic protons appear as two distinct unsymmetrical multiplets, centered at about δ = 6.80 and 7.18 p.p.m., whose integrated intensities correspond to five protons each.

Analysis of the stereochemical composition of the *crude* enamine by an examination of the n.m.r. and ultraviolet[25] spectra indicated the presence of 75% of the expected *cis*-enamine **9** and 25% of the unexpected *trans*-enamine **7**. Analyses *via* n.m.r. are approximate and were carried out in 1.5 *M* potassium *t*-butoxide in dimethyl sulfoxide by a comparison of the areas of the vinyl proton signals of the *cis*- and *trans*-enamines. Because of the proximity of the vinyl proton signals of the *cis*- and *trans*-enamines (a difference of 4 c.p.s. is observed in this solvent system) and the poorer resolution than observed in cyclohexane, a comparison of areas by triangulation methods was found more satisfactory than utilization of the integration signal. The method was shown to provide reproducible results and easily detect 5% of one stereoisomer in the presence of the other.

A 10% solution (approximate) of the pure *cis*-enamine **9** in 1.5 *M* potassium *t*-butoxide solution in dimethyl sulfoxide was kept at room temperature for 21 hr. The n.m.r. spectrum of the solution at end of 21 hr. indicated the presence of less than 5% (if any) of the corresponding *trans*-enamine **7**.

***trans*-1-(4-Morpholino)-1,2-diphenylethylene (7).**—All glassware was base washed and dried thoroughly prior to reaction. To 32 ml. of 1.5 *M* potassium *t*-butoxide solution in dimethyl sulfoxide was added 1.99 g. (0.0046 mole) of the *dl-threo* mesitoate ester **6b**. After stirring for 3 hr. at room temperature under a nitrogen atmosphere, the mixture was poured into 150 ml. of ice-cold water. The cloudy solution was extracted with ether and the organic layer was dried quickly over anhydrous potassium carbonate and evaporated *in vacuo* to yield 1.16 g. (94%) of crude solid, m.p. 78–81°. Recrystallization from methanol (temperature not permitted to exceed 50° to dissolve enamine and then the solution was quickly chilled) yielded 0.79 g. (65%) of an analytically pure crystalline solid, m.p. 103–104°, $\lambda_{max}^{cyclohexane}$ 240 mμ (ε 14,600) and 320 mμ (ε 11,400).

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.58; H, 7.42; N, 5.37.

The vinyl proton signal in the n.m.r. spectrum (cyclohexane) of the analytically pure sample appears as a sharp singlet (integrated intensity corresponding to one proton) at δ = 5.71 p.p.m. The aromatic proton region is broad (ranging from about δ = 7.0 to 7.6 p.p.m.) but appears to resolve into two unsymmetrical multiplets centered at about δ = 7.17 and 7.46 p.p.m. (integrated intensities correspond to eight and two protons, respectively). The fingerprint region of the infrared absorption spectrum is distinctly different from that of the *cis*-enamine **9**.

Analysis of the crude enamine by n.m.r. techniques indicated the presence of less than 5% (if any) of the corresponding *cis*-enamine **9**.

A 10% solution (approximate) of the pure *trans*-enamine **7** in 1.5 *M* potassium *t*-butoxide solution in dimethyl sulfoxide was kept at room temperature for 50 hr. The n.m.r. spectrum of the solution at end of 50 hr. indicated the presence of less than 5% (if any) of the corresponding *cis*-enamine **9**.

Preparation of the Morpholine Enamine of Desoxybenzoin by Direct Condensation of Morpholine and Desoxybenzoin.—A solution of 60.0 g. (0.30 mole) of desoxybenzoin, 39.2 g. (0.41 mole) of morpholine, and 0.1 g. of *p*-toluenesulfonic acid in 200 ml. of toluene was refluxed for 35 hr., after which time a quantitative yield of water had been collected in a water separator. The reaction mixture was neutralized with a freshly prepared solution of sodium methoxide in methanol. The toluene solution was washed with distilled water and dried over anhydrous potassium carbonate. Crystallization from methanol of the product obtained after removal of toluene yielded 60.0 g. (75%) of a pure crystalline solid, m.p. 90–92°. The infrared, ultraviolet, and n.m.r. spectra are identical in every detail with that of the *cis*-enamine **9** prepared *via* the elimination route.

Hydration of the *cis*-Enamine 9 *via* Hydroboration.—To a cooled (ice bath), carefully dried, three-neck flask fitted with drying tube, magnetic stirrer, and two pressure-equalizing addition funnels was added 0.500 g. (0.00189 mole) of the *cis*-enamine, 0.057 g. (0.00149 mole) of sodium borohydride, and 10 ml. of anhydrous tetrahydrofuran. From a dropping funnel 0.394 g. (0.00198 mole) of boron trifluoride etherate in 5 ml. of anhydrous

(24) Supplied by MSA Research Corp., Callery, Pa.

(25) The method of ultraviolet analysis used is described by H. H. Willard, L. L. Merrit, Jr., and J. A. Dean, "Instrumental Method of Analysis," 3rd Ed., D. van Nostrand Co., Inc., Princeton, N. J., 1958, p. 120.

tetrahydrofuran was added dropwise over a period of 20 min. to the well-stirred reaction mixture under a nitrogen atmosphere. The contents were then stirred at 0° for 2 hr. The resulting organoborane was oxidized without isolation by the simultaneous gradual addition to the contents of the flask at 0° of 2 ml. of 1 *N* sodium hydroxide solution and 2 ml. of 10% hydrogen peroxide solution. After completion of the addition the reaction was stirred at 0° for 15 min., poured into 20 ml. of water which was then saturated with sodium chloride and extracted with ether. The organic layer was dried over anhydrous calcium sulfate and evaporated to give rise to a product which was crystallized from ethanol to yield 0.114 g. (21%) of *dl-threo*-2-(4-morpholino)-1,2-diphenylethanol (**6a**), m.p. 150–151°. A gas chromatographic analysis of the filtrate revealed the presence of an additional 0.061 g. (11%) of the *dl-threo* amino alcohol **6a** (comparison to an authentic sample prepared from *cis*-stilbene oxide), 0.141 g. (28%) of 1-(4-morpholino)-1,2-diphenylethane (comparison to an authentic sample prepared by the catalytic reduction of the *cis*-enamine **9**), and *none* of the corresponding diastereomeric *dl-erythro*-2-(4-morpholino)-1,2-diphenylethanol (**8a**). The infrared spectrum of the isolated *dl-threo* amino alcohol **6a** was identical with that of the *dl-threo* amino alcohol derived from *cis*-stilbene oxide. A mixture melting point with the *dl-threo* amino alcohol derived from *cis*-stilbene oxide was undepressed.

Hydration of *trans*-Enamine 7 *via* Hydroboration.—The hydration was effected following the procedure outlined above for the *cis*-enamine **9**. A gas chromatographic analysis of the product obtained from 300 mg. (0.00113 mole) of the *trans*-enamine **7** indicated the presence of 64 mg. (20%) of the expected *dl-erythro* amino alcohol **8a** (comparison with an authentic sample prepared from *trans*-stilbene oxide), 43 mg. (13%) of the unexpected *dl-threo* amino alcohol **6a** (comparison with an authentic sample prepared from *cis*-stilbene oxide), and 77 mg. (26%) of 1-(4-morpholino)-1,2-diphenylethane.

The possibility that the *trans*-enamine **7**, m.p. 103–104°, employed in the hydration studies is contaminated with the *cis* isomer is considered unlikely in view of the sharpness of the melting point and the absence of a signal at $\delta = 5.56$ p.p.m. in the n.m.r. spectrum (cyclohexane) characteristic of the vinyl proton of the *cis*-enamine **9**.

The stability of the *dl-erythro* amino alcohol **8a** under the conditions of oxidation was demonstrated in the following way. To a solution of 30 mg. of *dl-erythro* amino alcohol **8a** in 5 ml. of tetrahydrofuran was simultaneously added 0.1 ml. of 1 *N* sodium hydroxide solution and 0.1 ml. of 10% hydrogen peroxide solution. The reaction was stirred for 15 min. at 0°, poured into 15 ml. of water, saturated with sodium chloride, and extracted with ether, and the organic layer was dried over anhydrous calcium sulfate. A gas chromatographic analysis of the product obtained after removal of the solvent indicated the presence of 27.8 mg. (93%) of the unreacted *dl-erythro* amino alcohol **8a**. No *dl-threo* amino alcohol **6a** could be detected.

It has also been observed that the unexpected *dl-threo* amino alcohol **6a** also arises when a freshly prepared solution of diborane in tetrahydrofuran, free of boron trifluoride, is employed in the hydroboration of the *trans*-enamine.

Isomerization of *trans*-1-(4-Morpholino)-1,2-diphenylethylene (7) to *cis*-1-(4-Morpholino)-1,2-diphenylethylene (9).—In each experiment, a solution containing the *trans*-enamine **7** in a concentration of 3.78×10^{-5} mole/l. in the indicated solvent (Table II) was prepared in a stoppered quartz cell (1-cm. path length), and the isomerization was followed for 25–35% consumption of *trans*-enamine in the absence of light at 25° in a Cary Model 14 recording spectrophotometer.

The isomer distribution is calculated by a standard method[25] making use of the known extinction coefficients in methanol: *cis*-enamine **9**, λ_{max} 303 mμ (ϵ 12,600) and 220 mμ (ϵ 14,600); *trans*-enamine **7**, λ_{max} 320 mμ (ϵ 11,300) and 240 mμ (ϵ 15,000). In each case duplicate runs were made, and a reasonable fit for a straight line was obtained in each case by plotting the time in minutes *vs.* the logarithm of the concentration of the *trans*-enamine **7**. The approximate first-order rate constants indicated in Table II are average values derived from the duplicate runs and were evaluated by multiplying the slope of the line by −2.303.

Determination of Equilibrium Composition.—A solution of the *trans*-enamine **7** (concentration of 3.78×10^{-4} mole/l.) in methanol was prepared and allowed to remain at 25° in the absence of light until no change was observed in the ultraviolet absorption spectrum for a period of 600 hr. (a total of 744 hr.). The equilibrium composition was then determined by ultraviolet spectroscopic techniques.[25] The accuracy of the method at equilibrium, ±2% for *cis* and ±2% for *trans*, was obtained by making three different determinations of the solution which had reached the equilibrium point. The equilibrium composition was verified by a similar procedure starting with the *cis*-enamine **9**. A solution of the *cis*-enamine **9** (concentration of 3.78×10^{-4} mole/l.) in methanol was allowed to remain at 25° in the absence of light for 744 hr. The ultraviolet spectroscopic analysis[25] indicated the same equilibrium composition as obtained starting with the *trans*-enamine **7**. The results are summarized in Table II.

Attempted Solvolysis of *dl-erythro*-2-(4-Morpholino)-1,2-diphenylethyl Mesitoate (8b) in Dimethyl Sulfoxide.—A solution of 100 mg. of the mesitoate ester **8b**, m.p. 193–194.5°, in 30 ml. of dimethyl sulfoxide was stirred at room temperature for 4 hr. The solution was poured into 75 ml. of water, saturated with sodium chloride, and extracted with ether. The ether extract was dried over anhydrous calcium sulfate. Evaporation of the dried ether extract *in vacuo* yielded 90 mg. (90% recovery) of the unreacted mesitoate ester, m.p. 192–194°. The infrared absorption spectrum is identical in every detail with that of authentic *dl-erythro* mesitoate ester.

Hydrolysis of *cis*- and *trans*-1-(4-Morpholino)-1,2-diphenylethylene.—A suspension of the *cis*- or *trans*-enamine in 10% aqueous hydrochloric acid was warmed on a steam bath for 20 min. The resulting clear solution was cooled to room temperature and extracted three times with ether. Evaporation *in vacuo* of the dried ether extract resulted in a 90–95% yield of desoxybenzoin, m.p. 54–55° (lit.[26] m.p. 55–56°). A mixture melting point with an authentic sample was undepressed.

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(26) "Handbook of Chemistry and Physics," 40th Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1958–1959, p. 950.