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Stereospecific and Stereoconvergent Rearrangement, Solvolysis and Elimination Reactions Involving Ethylenimonium Ketone Intermediates[1]

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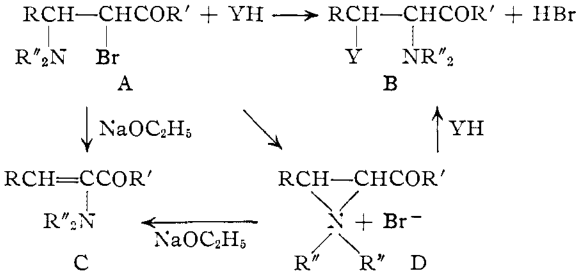
The *dl-threo-* and *dl-erythro-α*-bromo-β-morpholinobenzylacetophenones (Ia and Ib) can be rearranged under carefully selected conditions to yield β-bromo-α-morpholinobenzylacetophenones (IIIa or IIIb). Compounds Ia and Ib react with methanol to yield the *dl-threo-* and *dl-erythro-β*-methoxy-α-morpholinobenzylacetophenones (IVa and IVb). The rearrangement and rearrangement–methanolysis products IIIa, IIIb, IVa and IVb were evidently formed *via* the ethylenimonium ketone bromines IIa and IIb, which usually reacted in a stereospecific manner.

Compounds Ia, Ib and IIIb undergo dehydrobromination with sodium ethoxide to yield the known α-morpholino-*cis*-chalcone (Va). Compounds IIIa, IVa and IVb yielded the previously unknown α-morpholino-*trans*-chalcone (Vb) under the same conditions. Thus the bromides IIIa and IIIb may have given stereospecific *trans*-elimination reactions, but the elimination reactions of bromides Ia and Ib and the methoxy compounds IVa and IVb are stereoconvergent rather than stereospecific. Rate studies and stereochemical observations indicate that dehydrobromination of the bromides Ia and Ib involves attack of the base upon the ethylenimonium ketone bromides IIa and IIb.

Reactions of α-bromo-β-amino ketones of the type A, in which the amino function is tertiary, were investigated some years ago by Cromwell and his associates, and have more recently been studied in this Laboratory.

CHART I



It has been observed that these compounds react with amines,[3] with water[4] or with methanol[4] to yield products in which the bromine is replaced at the α-position by migration of the amino function, and the β-position is occupied by a nucleophilic group from the attacking reagent. The equation A → B, in which YH represents a nucleophilic reagent, describes these reactions in general terms. It has also been recognized[3] that dehydrobromination of the compounds A involves migration of the amino function to yield α-amino-α,β-unsaturated ketones of the type C.[5]

Cromwell and Cram,[3a] who first demonstrated the migration of the β-amino function by examining the structures of products obtained in reactions of type A compounds with amines, concluded that ethylenimonium ketone bromides (D), formed by neighboring group displacement of the α-bromine, must be intermediates in the rearrangement-displacement processes A → B. The rearrangement-elimination reactions A → C were explained in a similar fashion.[3,5]

Originally the α-bromo-β-amino ketones (A) were obtained by the addition of amines such as morpholine to α-bromo-α,β-unsaturated ketones.[3–7] More recently it has been discovered that other diastereoisomers could be obtained by adding N-bromomorpholine to an appropriate α,β-unsaturated ketone.[4,7] The availability of both *erythro* and *threo* isomers of compounds of the type A has made possible the investigation of steric effects in reactions of intermediate ethylenimonium ketone bromides (D) which is the subject of this paper. The results to be described here were obtained with compounds derived from morpholine and chalcone; *i.e.*, R and R′ in the above formulas were phenyl, and $R_2''N$– was the morpholino group. Evidence was presented previously that the isomer of type A prepared by morpholine addition to α-bromochalcone has the *threo* configuration.[7,8] The results of the present investigation strongly support this configurational assignment, as will become evident later in the discussion.

The investigation was concerned with: (1) rearrangement reactions, (2) methanolysis reactions and (3) elimination reactions. These three aspects of the work are interrelated, as indicated in Chart II, but will be discussed separately below under appropriate headings.

Rearrangement of the Diastereoisomeric α-Bromo-β-morpholinobenzylacetophenones (Ia and Ib).—As reported recently,[7] the assumed *dl-threo*-α-bromo-β-morpholinobenzylacetophenone (Ia) undergoes rearrangement to yield one of the β-bromo-α-morpholinobenzylacetophonones (IIIa) when refluxed for *ca.* 20 minutes in methanol. A more satisfactory method of obtaining the rearrangement product has been found since; if Ia is allowed to dissolve in a methanol–acetone mixture at room temperature, the resulting solution yields IIIa when concentrated by evaporation. As obtained in this manner the β-bromo compound

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(2) This paper is based principally on a thesis submitted by Yoon-Chai Lee in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the Carnegie Institute of Technology, August, 1961.

(3) (a) N. H. Cromwell and D. J. Cram, *J. Am. Chem. Soc.*, **65**, 301 (1943); (b) N. H. Cromwell and I. H. Witt, *ibid.*, **65**, 308 (1943). These papers include a review and interpretation of earlier work by Cromwell and others.

(4) P. L. Southwick and W. L. Walsh, *ibid.*, **77,** 405 (1955).

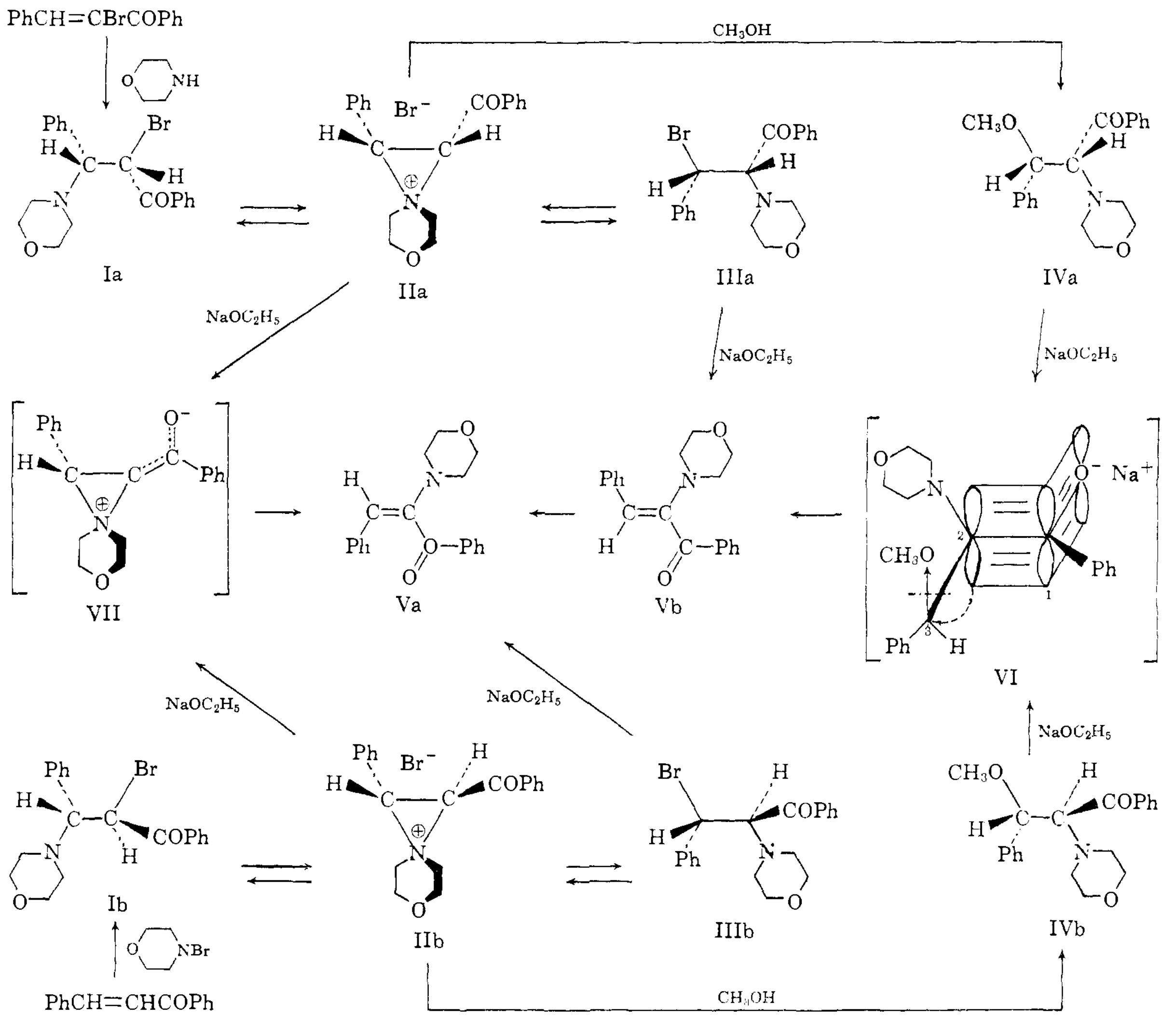
(5) N. H. Cromwell, *ibid.*, **62**, 2897 (1940).

(6) R. H. Jordan, R. E. Lutz and D. F. Hinkley, Jr., *J. Org. Chem.*, **16**, 1442 (1951).

(7) P. L. Southwick and R. J. Shozda, *J. Am. Chem. Soc.*, **81**, 5435 (1959).

(8) N. H. Cromwell, F. H. Schumacher and J. L. Adelfang, *ibid.*, **83**, 974 (1961), give a correlation with compounds of known configuration.

Chart II



IIIa is easily purified; there is no evidence of mixed diastereoisomers or methanolysis products.

When the assumed *dl-erythro* isomer Ib was treated with methanol under conditions identical to those used with Ia it was converted into a rearranged methanolysis product, as discussed below. However, by refluxing Ib in acetonitrile it was possible to obtain a rearranged product IIIb. That compound IIIb, like IIIa, was not an α-bromo ketone could be shown by its failure to oxidize acidified potassium iodide solutions.[9] The infrared spectrum of IIIb differed in a few details from that of its precursor Ib, but was essentially identical with that of IIIa.

It is evident that the ions of the ethylenimonium ketone bromides IIa and IIb recombine in suitable solvents to form the β-bromo-α-morpholino ketones IIIa or IIIb. On the question of whether rearrangement product IIIb represents a single configuration different from IIIa, the evidence is somewhat equivocal. The melting point of IIIb was lower (131° as compared to 138° for IIIa) but, due to decomposition on melting, mixed melting-point comparisons showing slight depression were probably not conclusive. One sample of IIIb, as discussed below, yielded α-morpholino-*cis*-chalcone (Va) when heated with sodium ethoxide under conditions which produced mainly α-morpholino-*trans*-chalcone (Vb) from IIIa. Another sample of IIIb, on the other hand, gave a mixture of Va and Vb, with the latter apparently predominating, when treated with sodium hydroxide in ethanol at 25°. The ultraviolet spectrum of the product mixture was virtually identical to that obtained from IIIa under the same conditions.

It might reasonably be assumed that, as in the case of related ethylenimines,[10] the ethylenimonium ions would be formed by a neighboring group displacement with inversion, and that the reaction with bromide ion which completes the rearrangement would likewise tend to produce inversion. Thus IIIa is shown as a *threo* compound and IIIb as an *erythro* compound. Some support for these configurational assignments is found in the

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[9] N. H. Cromwell and J. A. Caughlin, *J. Am. Chem. Soc.*, **67**, 2235 (1945).

[10] (a) N. H. Cromwell, G. V. Hudson, R. A. Wankel and P. J. Vanderhorst, *ibid.*, **75**, 5384 (1953); (b) F. H. Dickey, W. Fickett and H. J. Lucas, *ibid.*, **74**, 944 (1952); (c) G. K. Helmkamp and H. J. Lucas, *ibid.*, **74**, 951 (1952).

dehydrobromination experiments discussed below. The period of heating required for rearrangement of Ib to IIIb may in some experiments, however, have allowed IIIb to change over, at least in part, to the configuration of IIIa. More work is needed to establish whether the rearrangement of Ib in acetonitrile was stereospecific.

Methanolysis with Rearrangement of the Diastereoisomeric α-Bromo-β-morpholinobenzylacetophenones (Ia and Ib).—Previously the assumed *dl - erythro* - α - bromo - β - morpholinobenzylacetophenone (Ib) was found to yield a β-methoxy-α-morpholinobenzylacetophenone (IVb) when heated with methanol for *ca.* twenty minutes.[4] In the present investigation it was found that the bromomorpholino ketone Ib reacts rapidly with methanol even at 20°; apparently its half-life in a 1:1 methanol–acetone mixture at this temperature is less than five minutes, as judged by the amount of unchanged α-bromo ketone revealed by a rough quantitative method based upon reduction with acidified iodide solutions.[9] As already mentioned, the assumed *dl-threo*-isomer Ia, on the other hand, yielded mainly a rearrangement product (IIIa) rather than a rearranged solvolysis product when heated for a short time with methanol[7] or allowed to stand in a methanol–acetone solution. The rate of reaction of Ia in methanol is much slower than the rate of reaction of Ib; at 20° Ia appeared to have a half-life of *ca.* 120 minutes in the methanol–acetone mixture, as estimated by the same method used with Ib. The difference in the rates of reaction of the two isomers under these conditions can be attributed in part to a difference in the rate of formation of intermediate ethylenimonium bromides; as will be shown in the last section of this discussion, a "*cis* effect" retards the formation of the *cis*-ethylenimonium bromide IIa.[11]

By heating the *dl-threo*-α-bromo-β-morpholino ketone (Ia) in methanol for a longer period of time (*ca.* 5.5 hours proved sufficient) it was transformed, unquestionably *via* the rearrangement product IIIa to a large extent, into a β-methoxy-α-morpholinobenzylacetophenone (IVa). The latter product, m.p. 124.5–126°, was not identical with the diastereoisomer IVb, m.p. 116–117°, obtained from *dl-erythro*-α-bromo-β-morpholinobenzylacetophenone (Ib).[4] The two compounds displayed a large mixed-melting point depression and there were considerable differences in their infrared spectra in the "finger-print" region.

If the second β-methoxy-α-morpholino ketone (IVa) had resulted from a direct methanolysis of the rearranged bromide IIIa, it seems likely that a difficultly separable mixture of the diastereoisomers IVa and IVb would have resulted. That such was not the case suggests that the methanolysis proceeded primarily *via* attack of methanol on the *cis*-ethylenimonium ketone bromide IIa, which might be expected to be in equilibrium with the rearranged bromide IIIa. The rather unlikely possibility that IIIa was converted first into IVb and then into IVa by a thermodynamically favored epimerization can evidently be dismissed; IVb was unchanged by heating for 5.5 hours in refluxing methanol in the presence of hydrogen bromide (heating of IVb hydrobromide).

The stereospecificity of the methanolysis reactions of Ia (or IIIa) and Ib would seem to suggest that the *cis*- and *trans*-ethylenimonium ketone bromides IIa and IIb enjoy an appreciable configurational stability and that both undergo methanolysis by the same mechanism. A nucleophilic attack by methanol on the β-carbon of IIa or IIb with inversion of configuration is probably the most reasonable way in which to explain the preservation of the configurational difference with a considerable degree of stereospecificity. If this explanation is correct, the methanolysis product from Ia or IIIa would have the *threo* configuration IVa and that from Ib the *erythro* configuration IVb.

The fact that both of the methanolysis products IVa and IVb have the methoxyl group at the β-carbon was demonstrated by their conversion to an α-morpholinochalcone (Vb) by treatment with sodium ethoxide. There would be no reason to anticipate a rearrangement in these β-eliminations of methanol. The stereochemical implications of the result are considered in the second part of the next section.

Sodium Ethoxide-induced Elimination Reactions. Dehydrobromination of the β-Bromo-α-morpholinobenzylacetophenones IIIa and IIIb.—In the base-induced dehydrobromination of β-bromo ketones the degree of stereospecificity observed may be rather slight. Thus, for example, it is found that dehydrobromination of *erythro*-chalcone dibromides with sodium or potassium acetate yields both *cis*- and *trans*-α-bromochalcones with the *cis*-isomer in some cases the minor product, although it would be expected to predominate if the configuration of the product were controlled by a concerted *trans*-elimination mechanism.[12,13] (The *threo*-dibromides give the expected *trans*-α-bromochalcones.) Lutz, Hinkley and Jordan[12] have suggested that elimination *via* an intermediate enolate accounts for the low order of stereospecificity in such reactions.

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(11) (a) A review of "*cis* effects" has been published by D. Y. Curtin, *Record Chem. Progress*, (*Kresge-Hooker Sci. Lab.*), **15**, 111 (1954). (b) Since the rough reaction rate data under consideration here (unlike the more accurately determined elimination rate data discussed below) are in some particulars not fully consistent with other observations, it would probably be hazardous to attempt to draw any further conclusions from them. Thus, although the rate experiments with Ia at 20° in methanol and acetone indicated that the progress of the reaction had nearly ceased at *ca.* 50% conversion of Ia, suggesting possible equilibration of Ia with the rearrangement product IIIa, a preparative experiment carried out at room temperature apparently resulted in at least 94% conversion of Ia to IIIa. The conversion of Ib to IVb also appeared to become very slow at *ca.* 70% of completion in the rate experiments, but in this case it was to be expected that salt formation between liberated hydrogen bromide and starting material would exert a rate-retarding effect as the reaction progressed. The rough rate data on the rearrangement of Ia had another peculiarity; the reaction rate appeared to be greater during the second measured time interval than during the first. A more meaningful comparison of solvolysis rates could no doubt be obtained from separately prepared ethylenimonium ketone salts similar to IIa and IIb, but having an anion of sufficiently low nucleophilicity to permit their isolation. It now appears that ethylenimonium ketone perchlorates of this general type can be isolated and characterized (private communication from Dr. Nelson J. Leonard).

(12) R. E. Lutz, D. F. Hinkley, Jr., and R. H. Jordan, *J. Am. Chem. Soc.*, **73**, 4647 (1951).

(13) P. L. Southwick and R. J. Shozda, *ibid.*, **81**, 3298 (1959).

Dehydrobromination of the β-bromo-α-morpholinobenzylacetophenones IIIa and IIIb showed some stereospecificity. The α-morpholinochalcone, Va, m.p. 94°, obtained from one sample of IIIb was identical with the α-morpholinochalcone obtained earlier from either the *threo-* or the *erythro*-α-bromo-β-morpholinobenzylacetophenone (Ia or Ib),[4,5] but the product Vb, m.p. 76–78°, from the *threo* compound IIIa was the previously unknown geometrical isomer of Va.

The structure of the new α-morpholinochalcone (Vb) was established by the demonstration that it, like the other geometrical isomer Va, yielded benzyl phenyl diketone upon hydrolysis,[5] and by the observation that the isomer Vb reverted to the previously known isomer Va simply upon being allowed to stand at room temperature.[14] The ultraviolet spectrum of the new isomer Vb was similar to that of the known isomer Va. As measured in 95% ethanol, Va had its principal maximum at 259 mμ, ϵ 19,000, whereas the corresponding maximum for Vb was at 257 mμ, ϵ 16,150. Both had a very broad maximum of low intensity in the visible range; $\lambda_{\max}$ was 380 mμ, ϵ 1,520, for Va and 392 mμ, ϵ 2,270, for Vb. The most significant difference in the spectra of the two compounds was the location of absorptions appearing as shoulders on the long wave length side of the principal absorption bands. In the case of Va a shoulder at *ca.* 285 mμ, ϵ 16,000, indicated a band centered at *ca.* 287 mμ, $\epsilon \cong$ 14,000. In the case of Vb the shoulder was at *ca.* 300 mμ, ϵ 8,500, indicating a band centered at *ca.* 302 mμ, $\epsilon \cong$ 8,300. This latter band in Vb may represent a *trans*-chalcone absorption.[15]

The infrared spectra of the isomers Va and Vb were also similar, but significant differences were evident which could serve as the basis for configurational assignments. The carbonyl band in the previously known form is found at 5.97μ in carbon tetrachloride, whereas in the new isomer this absorption is at 6.04μ. Among α,β-unsaturated ketones those compounds which have substituents *cis* to the carbonyl function display carbonyl absorption at shorter wave lengths, due to steric interference with coplanarity in the conjugated system.[16] It has therefore been concluded that the new α-morpholinochalcone, m.p. 76–78°, probably has the *trans*-chalcone configuration Vb, the previously known isomer having the *cis*-chalcone configuration Va. These are the configurations expected to result if the previously assumed configurations of the diastereoisomeric β-bromo-α-morpholino ketones IIIa and IIIb are correct and the dehydrobrominations follow a *trans*-elimination mechanism.[17]

Stereoconvergent Methanol Elimination from the β-Methoxy-α-Morpholinobenzylacetophenones IVa and IVb.—When either of the diastereoisomeric β-methoxy-α-morpholinobenzylacetophones (IVa or IVb) was heated for 5 minutes with sodium ethoxide in ethanol, elimination of methanol occurred. In the case of both of the diastereoisomers IVa and IVb the isolated product was almost exclusively α-morpholino-*trans*-chalcone (Vb), although small amounts of the *cis*-isomer Va could be separated by careful fractional crystallization when heating was continued for 20 minutes. The configuration produced in these elimination reactions was apparently not the result of equilibration of isomers in the product, but the reactions cannot be regarded as stereospecific in the usual sense, since starting materials of differing configurations yield a product of the same configuration. Previously the term "convergent configuration control" was applied to this type of result.[7] The adjective "stereoconvergent" may be suggested as a convenient one-word designation for reactions characterized by convergent, kinetically determined, configuration control.[18]

The predominant isomer (Vb) formed from either starting material is that expected to result from *trans*-elimination of the elements of methanol from the *threo*-β-methoxy ketone IVa. Obviously a concerted *trans*-elimination is *not* involved in the formation of Vb from the *erythro*-β-methoxy ketone IVb, however, unless the elimination process occurs subsequent to isomerization of the *erythro*-β-methoxy ketone IVb into the *threo*-β-methoxy ketone IVa. Such an isomerization, if it occurred, would presumably depend upon formation in the basic reaction mixtures of an intermediate sodium enolate VI. The same enolate, which, of course, could also be derived from the *threo*-β-methoxy ketone IVa, would likewise

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(14) The possibility that this isomerization requires photochemical activation has not yet been investigated adequately, and the stability relationship of the two isomers in the absence of light is uncertain. Isomerization does not occur readily in refluxing ethanol alone, although there appears to be a rather slow conversion of Vb to Va (accompanied by decomposition) at the reflux temperature in ethanolic sodium ethoxide solution. The interesting isomerization in the solid state at room temperature deserves further investigation.

(15) (a) W. B. Black and R. E. Lutz, *J. Am. Chem. Soc.*, **77**, 5134 (1955); (b) A. Hassner and N. H. Cromwell, *ibid.*, **80**, 893 (1958); (c) R. D. Campbell and N. H. Cromwell, *ibid.*, **79**, 3456 (1957).

(16) E. A. Braude and C. J. Timmons, *J. Chem. Soc.*, 3756 (1955); see also refs. 15b and 15c.

(17) There is, however, a possibility that in neither instance is the predominant configuration of the elimination product actually determined by a *concerted trans* dehydrobromination. It is conceivable that dehydrobromination of the *erythro* isomer IIIb might proceed *via* the ethylenimonium ketone bromide IIb and that dehydrobromination of the *threo* isomer IIIa might proceed *via* a bromo enolate analogous to the methoxy enolate pictured in formula VI. The results would still indicate that the configurational assignments to IIIa and IIIb were correct, however, since if either isomer reverted rapidly to an ethylenimonium ketone bromide and was thus converted to α-morpholino-*cis*-chalcone (Va) it is the *erythro* isomer which would be expected to do so.

(18) (a) Eliel, in elaborating an earlier suggestion by Zimmerman (*J. Am. Chem. Soc.*, **81**, 108 (1959)), has recently advocated the use of "stereoselective" as a general term defined in such a way as to embrace not only stereospecific reactions, in which the configuration of the starting material influences the configuration of the product, but also those reactions (for which he does not suggest any special term) displaying what we have called "convergent configuration control" in ref. 7 (See E. L. Eliel, "Stereochemistry of Organic Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 436.) "Stereoselective reactions," if defined as suggested by Eliel, might appropriately be subclassified as either stereospecific or stereoconvergent when it can be determined whether the configurational outcome is dependent upon, or independent of, the configuration of the starting material. (b) Recent investigations have revealed analogous behavior in other base-induced elimination reactions. See, for example, the case of the 2-chloro-1,2-diphenylethyl *p*-tolyl sulfones studied by S. J. Cristol and P. Pappas, Abstracts of the 140th Meeting of the American Chemical Society, Chicago, Ill., September 3 to 8, 1961, p. 16-Q. S. J. Cristol and R. S. Bly, Jr., *J. Am. Chem. Soc.*, **82,** 143 (1960), provide a recent review and discussion of work on steric effects in base-induced dehydrohalogenations; see also ref. 19b.

be an intermediate in a non-concerted methanol elimination. Thus, it is not necessary to assume a completed isomerization of the *erythro*-β-methoxy ketone IVb in order to account for the formation of the α-morpholino-*trans*-chalcone Vb; it is quite possible that the sodium enolate VI, whether produced from IVa or IVb, would yield principally the α-morpholino-*trans*-chalcone Vb when the elimination is completed by loss of methoxide ion. If resonance in the enolate anion tended to stabilize a planar configuration about a partial double bond between the α-carbon and the carbonyl carbon, then the normal tendency for steric interactions to be minimized would result in the "overlap control" suggested by Zimmerman[19] (see formula VI[20]), and the expected product from the non-concerted elimination would be the observed α-morpholino-*trans*-chalcone (Vb).

Direct Dehydrobromination of Intermediate Ethylenimonium Ketone Bromides (IIa and IIb).—Treatment of either of the *dl-threo*[5]- or *erythro*[4]-α-bromo-β-morpholinobenzylacetophenones (Ia or Ib) with sodium ethoxide results in the formation of the compound now considered (*vide supra*) to be α-morpholino-*cis*-chalcone (Va). Thus the elimination reactions of these compounds, which occur under conditions that do not appreciably interconvert Va and Vb, are not stereospecific, but stereoconvergent.

The work of Cromwell and Cram[3a] provided evidence that these dehydrobrominations necessarily involve intermediate formation of an ethylenimonium ketone bromide, but it has not heretofore been established whether the base acted directly on the ethylenimonium ion, as was originally suggested,[3] or on rearrangement or solvolysis products such as IIIa or the ethoxy analog of IVa. It has now become evident from consideration of the results presented above that the ethylenimonium bromide IIa derived from the *threo*-α-bromo-β-morpholino ketone Ia must be directly attacked by sodium ethoxide, since the dehydrobromination of Ia yielded α-morpholino-*cis*-chalcone (Va), whereas dehydrobromination of the rearrangement or methanolysis products IIIa or IVa yielded α-morpholino-*trans*-chalcone (Vb).

The fact that dehydrobromination produces α-morpholino-*cis*-chalcone (Va) from either the *cis*- or the *trans*-ethylenimonium ketone bromides IIa or IIb indicates that at some stage in the reaction process an intermediate or transition state occurs in which the original configurational difference is lost. An intermediate enolate zwitterion (VII) represents an interesting possibility of this kind. It is not clear, however, why the collapse of such a zwitterion should result in a high degree of convergent configuration control to yield essentially only the *cis* form of α-morpholinochalcone (Va).[21]

Sodium ethoxide attack upon the ethylenimonium ketone bromides IIa and IIb must be rapid enough to intercept these intermediates before they can undergo rearrangement or solvolysis. It might therefore be surmised that the rate-controlling step in dehydrobromination with excess base should be formation of the intermediates IIa or IIb; the steady-state approximation should be applicable to concentrations of IIa and IIb, and rates of formation of the elimination product Va should approach closely the rates of formation of IIa and IIb.

In order to examine this possibility, the rates of dehydrobromination of the α-bromo-β-morpholino ketones Ia and Ib at 25° by the action of sodium hydroxide in ethanol solution were measured by an ultraviolet spectrophotometric method. The reactions were found to follow a first-order rate equation with respect to Ia and Ib, and the rates were not increased by doubling the concentrations of sodium hydroxide. (Sodium hydroxide concentrations were either five or ten times the molar concentrations of Ia or Ib.) It is believed, therefore, that the measured dehydrobromination rates reveal the rates of formation of the ethylenimonium ketone bromides IIa and IIb. The very rapid reaction rates led to difficulties in obtaining accurately reproducible data; the half-lives of the *erythro* and *threo* compounds Ib and Ia were only 54 and 200 seconds, respectively, under the conditions used. However, the quality of the data was adequate to demonstrate unmistakably that the rate of formation of the assumed *trans*-ethylenimonium ketone bromide IIb (k_1 = *ca.* 12.6×10^{-3} sec.$^{-1}$) was much greater than that for the assumed *cis* isomer IIa (k_1 = *ca.* 3.53×10^{-3} sec.$^{-1}$).

It has been concluded, on the basis of these results, that formation of the *cis*-ethylenimonium ketone bromide IIa shows the expected rate retardation due to steric interactions (*cis*-effect) between the phenyl and benzoyl groups, and that dehydrobromination rate studies supply additional strong support for the previous configurational assignments to compounds Ia and Ib. With these configurations firmly established it is possible to attach more importance to suggestions[7] which have been made regarding the manner in which configuration control might be exercised in the formation of Ia and Ib by the conjugate addition reactions of morpholine or N-

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[19] See (a) H. E. Zimmerman, L. Singer and R. S. Thyagarajan, *J. Am. Chem. Soc.*, **81**, 108 (1959); (b) H. E. Zimmerman and L. Ahramjian, *ibid.*, **81**, 2086 (1959); (c) H. E. Zimmerman and L. Ahramjian, *ibid.*, **82**, 5459 (1960). "Overlap control" evidently represents an important influence favoring stereoconvergent results in elimination reactions leading to conjugated systems.

[20] Formula VI is intended to represent a configuration and conformation in which the four bonds attached to the C_1 to C_2 enolate double bond lie in a plane perpendicular to the plane determined by the bonds between C_2 and C_3 and between C_3 and the methoxyl oxygen. Transition state geometry of this kind has been assumed[19b] to prevail in the dehydration of the *erythro*- or *threo*-3-hydroxy-2,3-diphenylpropionic acids and related compounds under conditions used in the Perkin reaction. The selection of VI as the most reasonable picture of a favored configuration and conformation which would lead to the transition state for elimination of methoxide ion is based upon examination of steric interactions in molecular models of both geometrical isomers of the enol form of β-methoxy-α-morpholinobenzylacetophenone. The geometry indicated by VI would appear to minimize these interactions.

[21] It is possible that collapse of a zwitterion of the type VII would be directed almost exclusively toward formation of α-morpholino-*cis*-chalcone (Va) because this would allow an immediate release of crowding between the spiromorpholino group and the phenyl at the β-carbon which would be present in the ethylenimonium ketone bromide or the zwitterion VII.

bromomorpholine indicated in Reaction Chart II. The configurations are those required by the hypothesis that in the conjugate additions intermediate chelated β-amino enols are formed and then ketonized by protonation or bromination from the less hindered side of the chelate ring.[7]

NOTE ADDED IN PROOF.—Recently, nuclear magnetic resonance measurements have provided evidence regarding the configurations of Ia and Ib which is not dependent on the interpretation of any reaction process. In the spectrum of Ib, as compared to that of Ia and appropriate related compounds, the lines assignable to the two oxygen-linked methylenes of the morpholino group are moved *ca.* 0.5 p.p.m. to higher field, an effect which probably must be attributed to long-range shielding by a phenyl group. The most favorable conformation of the *erythro* configuration would place the benzoyl group *gauche* to the morpholino group, and, as models indicate, the phenyl portion of the benzoyl group would then be properly located to exert a diamagnetic effect such as that observed in the spectrum of Ib (unpublished observations by P. L. Southwick and G. E. Milliman).

Experimental[22,23]

Rearrangement of *dl-threo-* and *dl-erythro-α*-Bromo-β-morpholinobenzylacetophenones (Ia and Ib). Preparation of *dl-threo-β*-Bromo-α-morpholinobenzylacetophenone (IIIa).—A mixture of 2 g. (0.0053 mole) of *threo-α*-bromo-β-morpholinobenzylacetophone (Ia), 50 ml. of acetone and 125 ml. of methanol was stirred vigorously at room temperature for a period of 8 hours, while the starting material gradually dissolved. Aqueous sodium bicarbonate (30 ml.) was then added to the solution. A yellow solid immediately precipitated. The mixture was kept at 0° for 2 hours. The solid was removed by filtration and crystallized from petroleum ether (b.p. 65–110°). Pale-yellow needles (0.82 g., m.p. 138–139° dec.) were obtained. The volume of the mother liquor from the crystallization was then reduced to half by evaporation under reduced pressure and an additional 1.05 g. of the same yellow product, m.p. 138.5–140° dec., separated. The total amount of the rearrangement product obtained was 1.87 g. (94% yield). The infrared spectrum of this material was identical with that of an authentic sample, m.p. 134–137° dec.,[7] and did not show the band corresponding to a methoxyl group (9.10 μ) which indicates the presence of a methanolysis product in certain samples prepared by refluxing Ia in methanol; infrared spectrum (in chloroform): 3.40(70), 3.51(67), 5.96(38), 6.23(64), 6.32(70), 6.70(72), 6.89(47), 7.27(65), 7.35(66), 7.56(60), 7.72(53), 7.87(55), 8.04(56), 8.49(57), 8.74(47), 8.98(20), 9.34(59), 9.72(64), 9.95(54), 10.30(62)b, 10.90(63), 11.51(49), 11.82(64)sh.

A 1-g. sample of the compound treated with acidified potassium iodide as described by Cromwell and Caughlin[9] yielded only a trace of iodine. Only 0.3 ml. of 0.03 *N* thiosulfate was required for its titration.

Rearrangement Product (IIIb) of *dl-erythro-α*-Bromo-β-morpholinobenzylacetophenone (Ib).—Commercial acetonitrile was treated with sodium carbonate until gas evolution ceased. The acetonitrile was then distilled from phosphorus pentoxide. The freshly distilled acetonitrile (50 ml.) and 3.8 g. (0.01 mole) of *erythro-α*-bromo-β-morpholinobenzylacetophenone, m.p. 132–134°,[4] were refluxed for 2.5 hours in an apparatus protected from moisture, and then left at room temperature for 12 hours. The acetonitrile was removed by evaporation under reduced pressure. The dark-brown residue was extracted several times with boiling petroleum ether (b.p. 65–110°) and the extracts combined. The petroleum ether solution was evaporated to dryness and the residue air-dried. The crude rearrangement product, m.p. 121–124°, weighed 2.5 g. The brown residue remaining after the petroleum ether extraction contained starting material.

The melting point of the rearrangement product was not raised by recrystallization from petroleum ether unless the admixed starting material was removed by methanolysis. To 50 ml. of boiling methanol was added 2 g. of the crude rearrangement product and the solution heated for 5 to 7 minutes. The solution was immediately cooled by evaporation under reduced pressure, causing the rearrangement product to be precipitated. After evaporation had reduced the volume to one-half, 1.2 g. of a flaky white solid was collected by filtration. One recrystallization from petroleum ether (b.p. 65–110°) yielded the pure product, m.p. 130–131° dec.; infrared spectrum (in chloforom): 3.40(75), 3.52(76), 5.10(96), 5.99(42), 6.26(76), 6.32(84)sh, 6.71(87), 6.91(56), 7.30(86), 7.58(72), 7.74(63), 7.90(70), 8.06(63), 8.76(65), 8.99(30), 9.38(83), 9.72(83), 9.96(67), 10.40(80), 10.88(82), 11.53(61), 11.80(80).

Anal. Calcd. for $C_{19}H_{20}I_2NBr$: C, 60.97; H, 5.39; N, 3.74. Found: C, 61.42; H, 5.60; N, 3.73.

Admixture of this compound with the starting material produced a depression of the melting point to 122–125° dec. The m.p. of a mixture with IIIa was 124–127° dec. The test with acidified potassium iodide showed that at most not more than a trace of α-bromo ketone was present.

Infrared Spectra of *dl-threo* and *dl-erythro-α*-Bromo-β-morpholinobenzylacetophenones (Ia and Ib).—The preparation of these compounds has been described previously,[4–6] but infrared data had not been recorded and are given here for comparison with rearrangement products IIIa and IIIb; spectrum of the *threo*-isomer (Ia) (in chloroform): 3.46(76), 3.56(76), 5.93(34), 6.27(74), 6.34(82), 6.72(85), 6.92(52), 7.24(92)sh, 7.32(81), 7.39(78), 7.53(78), 7.61(77), 7.76(70), 7.93(50), 8.50(79), 8.80(68), 9.00(28), 9.19(84), 9.70(92)b, 9.94(81)sh, 10.20(64), 10.88(79), 11.48(62); spectrum of the *erythro*-isomer Ib (in chloroform): 3.29(74)sh, 3.40(62), 3.54(59), 5.96(25), 6.26(54), 6.34(63), 6.92(34), 7.35(56), 7.57(51), 7.74(57), 7.93(39), 8.06(49), 8.56(55), 8.77(41), 9.01(11), 9.40(52), 9.76(60), 10.00(40), 10.26(46), 10.90(57), 11.37(52), 11.67(49), 12.00(62).

Methanolysis of *dl-threo* and *dl-erythro-α*-Bromo-β-morpholinobenzylacetophenones (Ia and Ib). Preparation of *dl-threo-β*-Methoxy-α-morpholinobenzylacetophenone (IIIa).—Five grams of *threo-α*-bromo-β-morpholinobenzylacetophenone (Ia, m.p. 131–132°) and 70 ml. of absolute methanol were refluxed for 5.5 hours. The solution was cooled to room temperature, and poured into 140 ml. of a saturated sodium bicarbonate solution. The mixture was placed in a refrigerator for 2 hours and the yellow crystals which separated were removed by filtration and crystallized from petroleum ether (b.p. 65–110°). The yield was 3.2 g. (70%), m.p. 123–126°. Following several recrystallizations from the same solvent, 2.8 g. (60%) of the compound was obtained as stout, colorless to pale yellow needles, m.p. 124.5–126°. A mixture of this compound with the previously described[4] *dl-erythro-β*-methoxy-α-morpholinobenzylacetophenone (m.p. 116–117°) showed a depression to 108–112°; infrared spectrum (in carbon tetrachloride): 3.30(65)sh, 3.42(63), 3.52(62), 5.94(34), 6.23(76), 6.32(84), 6.70(80), 6.90(53), 7.30(77), 7.40(76), 7.48(74), 7.58(77), 7.64(80), 7.76(67), 7.89(75), 8.04(67), 8.24(70), 8.40(65), 8.48(57), 8.64(70), 8.76(58), 8.95(20), 9.10(28), 9.12(67), 9.72(83), 9.86(82), 10.00(77), 10.16(47), 10.78(78), 10.86(65), 11.52(53).

Anal. Calcd. for $C_{20}H_{23}O_3N$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.88; H, 7.29; N, 4.49.

Preparation of *dl-erythro-β*-Methoxy-α-morpholinobenzylacetophenone (IIIb).—The first procedure, similar to that described by Southwick and Walsh,[4] is given for comparison with the second (room temperature) procedure. One and one-half grams (0.0046 mole) of *erythro-α*-bromo-β-morpholinobenzylacetopehone (Ib) (melting point 134–135°) was dissolved in 20 ml. of absolute methanol. This solution was heated on a steam-cone for about 20 minutes. Distilled water (20 ml.) was added to the solution and the precipitate was filtered out. Sodium bicarbonate was added to the filtrate and additional crude β-methoxy-α-morpholinobenzylacetophenone was precipitated. This was combined with the first portion. The total crude yield was 1 g. (77%). The crude material was recrystallized twice from petroleum

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[22] Microanalyses by Drs. G. Weiler and F. B. Strauss, Oxford, Eng., and Geller Microanalytical Laboratories, Bardonia, N. Y.

[23] Infrared spectra were determined with a Perkin-Elmer model 21 spectrophotometer equipped with rock-salt optics. Solutions usually contained 40 mg. of sample per ml. of solution. Figures listed are wave lengths of absorption bands in microns, followed by the percentage transmittance (figure given in parentheses). Absorptions which appear as shoulders on other bands are indicated by the notation sh, very broad absorptions by b. Ultraviolet spectra were measured with a Cary recording spectrophotometer or with a Beckman spectrophotometer, model DU.

ether (b.p. 65–110°) to yield light-yellow prisms, m.p. 116–117° (reported[4] m.p. 116–117°).

In another experiment 2 g. of compound Ib was dissolved in 50 ml. of methanol at room temperature during a period of 25 minutes with continuous shaking. When worked up as in the experiment described above, 1.4 g. (80%) of crude product was obtained which yielded the same compound, m.p. 116–117°, after crystallization from petroleum ether; infrared spectrum (in carbon tetrachloride): 3.30(80), 3.40(59), 3.54(60), 5.96(30), 6.25(73), 6.32(82), 6.70(84), 6.90(42), 7.28(76), 7.48(71), 7.56(72), 7.64(74)sh, 7.74(64), 7.91(68), 8.03(63), 8.22(44), 8.36(72)sh, 8.44(70), 8.49(71), 8.62(59), 8.74(69)sh, 8.96(17), 9.04(29)sh, 9.22(58)sh, 9.32(70)sh, 9.56(68), 9.68(75)sh, 9.74(73), 9.88(68), 10.00(81), 10.32(63), 10.90(79), 11.00(77), 11.34(80), 11.56(64).

Approximate Rearrangement and/or Solvolysis Rates of the α-Bromo-β-morpholinobenzylacetophenones (Ia or Ib) in Methanol and Acetone at 20°.—The reaction vessel was a 1-l. flask equipped with a mechanical stirrer and a thermometer, which was placed in a constant temperature bath at 20 ± 0.5°. The α-bromo-β-morpholinobenzylacetophenone (Ia or Ib, 2.00 g.) was placed in the flask and dissolved in 200 ml. of dry acetone which had been cooled to 20°. The reaction was started by addition of 200 ml. of absolute methanol which had been maintained at 20°. Aliquot portions (20 ml.) of the solution were then removed at appropriate time intervals. To these aliquots were added 16 ml. of 0.2 *N* potassium iodide and 0.6 ml. of 3 *N* hydrogen chloride in dry methanol, and the mixtures were allowed to stand at 20° for 25 minutes. Water (50 ml.) and 2 ml. of a 2% starch indicator solution in water were added to these mixtures, which were then immediately titrated with 0.030 *N* sodium thiosulfate to a colorless end-point.[9]

TABLE I

dl-threo-α-BROMO-β-MORPHOLINOBENZYLACETOPHENONE (Ia)

Time of reaction, minutes	Ml. 0.030 *N* sodium thiosulfate (av. 3 runs)	Fraction of α-Bromo ketone remaining
Start	16.5	1.00
20	15.7	0.95
40	13.4	.81
60	11.5	.70
80	10.3	.62
100	8.9	.54
120	8.2	.50
140	8.2	.50

At the end of one run the remaining solution was treated with an equal volume of distilled water, and made alkaline with saturated sodium bicarbonate. The product, collected by filtration and crystallized from petroleum ether (b.p. 65–110°), proved to be *dl-threo*-β-bromo-α-morpholinobenzylacetophenone (IIIa).

TABLE II

dl-*erythro*-α-BROMO-β-MORPHOLINOBENZYLACETOPHENONE (Ib)

Time of reaction, minutes	Ml. 0.030 *N* sodium thiosulfate (av., 3 runs)	Fraction of α-Bromo ketone remaining
Start	14.4	1.00
2	9.2	0.64
5	5.4	.38
10	4.5	.31
15	4.0	.28
20	4.1	.28
30	4.1	.28

Dehydrobromination of *dl-threo* and *dl-erythro*-β-Bromo-α-morpholinobenzylacetophenones (IIIa and IIIb). Preparation of α-Morpholino-*trans*-chalcone (Vb) from IIIa.—*dl-threo*-α-Morpholino-β-bromobenzylacetophenone (IIIa), m.p. 138–140°, (3.8 g., 0.01 mole) was added to a boiling sodium ethoxide solution prepared by dissolving 0.23 g. (0.01 mole) of sodium in 10 ml. of absolute ethanol. The mixture immediately developed an orange-yellow color and a white precipitate (sodium bromide) settled out. Heating under reflux was continued for 7 minutes. The mixture was immediately cooled and diluted with ether. The sodium bromide was removed by filtration, the ether solution was dried over magnesium sulfate, and the ether was evaporated under reduced pressure. Recrystallization of the residual solid from 95% ethanol, gave bright yellow needles (2.1 g., 71%), m.p. 76–77° dec. The analytical sample, obtained after further recrystallization from ethanol, melted at 76–78°; infrared spectrum (in carbon tetrachloride): 3.22(73), 3.35(60), 3.48(54), 6.04(21), 6.21(50), 6.30(68)sh, 6.69(65), 6.89(31), 6.99(61), 7.15(53), 7.28(58), 7.32(65)sh, 7.53(57), 7.68(60), 7.95(28), 8.02(21), 8.49(47), 8.65(38), 8.92(11), 9.29(59)sh, 9.35(55), 9.58(42), 9.72(53), 9.98(61), 10.16(24), 10.80(51), 11.45(54), 11.78(51), 13.93(32), 14.42(21), 14.75(55); ultraviolet spectrum (in 95% ethanol): maxima: 257 mμ, ε 16,150 (shoulder at 300 mμ, ε 8,500); 392 mμ, ε 2,270; minima: 227 mμ, ε 9,000; 350 mμ, ε 1,540.

Anal. Calcd. for $C_{19}H_{19}NO_2$: C, 77.90; H, 6.49; N, 4.78. Found: C, 77.56; H, 6.52; N, 4.90.

Hydrolysis of α-Morpholino-*trans*-chalcone.—Three grams of α-morpholino-*trans*-chalcone, m.p. 76–78°, was heated under reflux for 25 minutes in 30 ml. of 15% sulfuric acid. No odor of benzaldehyde was noted. An oil which separated from the mixture was taken up in ether. The ether solution was washed with water three times and dried over magnesium sulfate. The ether was removed under reduced pressure to leave a residual oil and some colorless needles. The solid fraction melted at 61–63° after two recrystallizations from aqueous acetone (benzyl phenyl diketone is reported[5] to melt at 61–63°).

To a solution of 2 g. of the oil fraction in 10 ml. of ethanol was added 0.97 g. of *o*-phenylenediamine and the mixture was warmed gently on a steam-cone for a few minutes. The mixture was left at room temperature for 2 hours. The precipitated white needles were removed by filtration and recrystallized from aqueous acetone to yield 2.3 g. (80%) of the quinoxaline, m.p. 98–99°. Admixture of the quinoxaline derivative[5] of the diketone obtained by hydrolysis of α-morpholino-*cis*-chalcone (Va) with the above product produced no depression of melting point (m.p. 98–99°).

Preparation of α-Morpholino-*cis*-chalcone (Va) from IIIb.—Five grams (0.013 mole) of the rearrangement product IIIb was treated with 0.46 g. (0.02 mole) of sodium dissolved in 13 ml. of absolute ethanol as in the experiment with IIIa above. Refluxing was continued for 15 min. Processing of the mixture as described above yielded 3.5 g. (89%) of product, which after two crystallizations from ethanol was obtained as orange plates, m.p. 92–94°; infrared spectrum (in carbon tetrachloride): 3.27(82), 3.30(82), 3.38(70), 3.50(67), 5.97(29.5), 6.24(30), 6.35(66), 6.70(87), 6.91(36), 7.24(53), 7.48(81.5), 7.68(75), 7.89(29), 8.12(30), 8.22(39), 8.36(41), 8.52(51)s, 8.57(47), 8.62(66)s, 8.91(18), 9.36(82), 9.56(83), 9.74(78), 9.99(82), 10.21(30),10.73(74), 10.95(75), 11.20(82)s, 11.35(73), 11.47(72); ultraviolet spectrum (in 95% ethanol): maxima: 259 mμ, ε 19,000 (shoulder at 285 mμ, ε 16,000); 380 mμ, ε 1,520; minima: 229 mμ, 8,900; 340 mμ, ε 1,070. The compound was identical with the product obtained from compound Ia.[5]

Isomerization Experiments with α-Morpholino-*trans*-chalcone (Vb).—(a) Three grams (0.01 mole) of α-morpholino-*trans*-chalcone, m.p. 75–77.5°, in a 25-ml. erlenmeyer flask was illuminated for 36 hours with a reflector infrared lamp (G.E. 250 watt, 115 volt) placed at a distance of about 18 inches. The yellow solid slowly melted and turned to a reddish gel. The gel was crystallized twice from 95% ethanol to yield 2.0 g. (67%) of orange plates, m.p. 92–94°. A mixed melting point with a sample of the higher-melting *cis* form of α-morpholinochalcone showed no depression (m.p. 92–94°) and the infrared spectra were the same.

(b) Three grams (0.01 mole) of α-morpholino-*trans*-chalcone (Vb) in an 8-mm. clear glass vial was allowed to stand in the laboratory for 3 weeks with occasional shaking. The bright yellow color gradually turned to orange. Following three crystallizations from 95% ethanol, orange plates, m.p. 91–93°, were obtained. The substance showed no depression of the melting point when mixed with a sample of the higher-melting *cis* form of α-morpholinochalcone (Va).

(c) Six grams (0.02 mole) of α-morpholino-*trans*-chalcone (Vb) was added to a boiling sodium ethoxide solution prepared by dissolving 0.92 g. of sodium in 20 ml. of absolute ethanol. The mixture was heated under reflux for 20 minutes. To the cooled solution 30 ml. of water was added and the mixture was extracted with ether. The ether solution was evaporated under reduced pressure. The resulting reddish gel was crystallized twice from aqueous ethanol to yield 1.0 g. (15%) of orange plates, m.p. 92–94°. A mixed melting point with α-morpholino-*cis*-chalcone (Va) was not depressed. Four grams of red oil which resisted crystallization remained.

(d) When 1.0 g. of α-morpholino-*trans*-chalcone (Vb) was refluxed for 24 hours in 20 ml. of ethanol, 0.9 g. of starting material, m.p. 76–78° dec., was recovered.

Methanol Elimination from *dl-threo-* and *dl-erythro-β*-Methoxy-α-morpholinobenzylacetophones (IVa and IVb). Elimination from the *threo*-Isomer IVa. Five-minute Reaction Period.—*dl-threo-β*-Methoxy-α-morpholino-benzylacetophenone (IVa) (5 g., 0.016 mole) was added to a boiling sodium ethoxide solution prepared by dissolving 0.47 g. (0.02 g. atom) of sodium in 10 ml. of absolute ethanol. Heating under reflux was continued for 5 minutes. The solvent was immediately evaporated at reduced pressure without heating. The residual oil was washed with water and crystallized from ethanol to yield 2.6 g. (54%) of yellow needles, m.p. 75–78°. The product melted at 76–78° after recrystallization from ethanol and was shown by mixed melting point to be the same as samples of α-morpholino-*trans*-chalcone (Vb) prepared from IIIa.

Twenty-minute Reaction Period.—The experiment described above was duplicated except that heating under reflux was continued for 20 minutes. The residual oil, a mixture of the *cis* and *trans* isomers, was washed with water. The water was decanted and the residual oil was dissolved in hot 95% ethanol. A red oil separated at the bottom of the flask when the mixture was cooled. The mixture was poured into a separatory funnel and the oil was separated from the upper layer of solution. Cooling of the upper layer in the refrigerator caused separation of additional oil. The red oils were combined and crystallized from aqueous ethanol to yield α-morpholino-*cis*-chalcone (Va) as orange plates, m.p. 91–93°. The yield was 0.6 g. (13%). The ethanol solutions from which the oil had separated, when concentrated by evaporation and cooled, yielded α-morpholino-*trans* chalcone (Vb) as yellow needles, m.p. 75–78°, yield 2.2 g. (49%).

Elimination from the *erythro* Isomer IVb. Five-minute Reaction Period.—The same procedure as described above for *threo* isomer was followed with the same amounts of materials. The product was exclusively the *trans* isomer Vb, yellow needles, m.p. 75–78°, yield 2.2 g. (48%).

Twenty-minute Reaction Period.—The same procedure as described above for the *threo* isomer was followed again with the same amounts of materials. The separation procedure was also the same. In one run the yield of *cis* isomer was 0.1 g. (2%) and of *trans* isomer 1.8 g. (40%).

Dehydrobromination of *dl-threo-* and *dl-erythro*-α-Bromo-β-morpholinobenzylacetophenones (Ia and Ib). Preparation of α-Morpholino-*cis*-chalcone (Va) from Ia or Ib.—*dl-threo*-α-Bromo-β-morpholinobenzylacetophenone (Ia) (10 g., 0.027 mole) was dropped into a boiling sodium ethoxide solution prepared by dissolving 0.92 g. of sodium in 26 ml. of absolute ethanol. Heating under reflux was continued for *ca.* 4 minutes until a white precipitate formed. The mixture was rapidly cooled to 0° by addition of ice and was then extracted with ether. The ether solution was dried over magnesium sulfate and the ether evaporated. Three crystallizations of the residue from 95% ethanol yielded 6.4 g. (81% yield) of orange plates, m.p. 90–93°. One more recrystallization raised the melting point to 94–96°. Cromwell[5] reported the m.p. 94–96° for the product prepared in the same manner but with a longer heating period (20 minutes). An extended heating period appeared to reduce the yield.

A similar experiment with *dl-erythro*-α-bromo-β-morpholinobenzylacetophenone (Ib) in which the same quantities of materials were used but heating was extended to 10 minutes gave a somewhat lower yield (5.6 g., 70%) of a less pure product (m.p. 88–92°). The m.p. reached only 90–93° after a total of four crystallizations.

Dehydrobromination Rates.—All runs were conducted with 6.00 × 10^{-5} mole (0.0225 g.) quantities of the bromomorpholino ketones Ia and Ib. The samples were weighed into a one-liter volumetric flask. Methylene chloride (25 ml.) was then added to dissolve the sample and thereby avoid delay in getting the compound dissolved when mixed with the ethanol solution containing the base. The volume of the reaction solution was made up to 1 liter by addition of ethanolic sodium hydroxide prepared by diluting 5.00-ml. quantities of aqueous sodium hydroxide of known concentration to 1 liter with 95% ethanol. The ethanolic sodium hydroxide was brought to 25.00 ± 0.010° before use. The reaction solutions were mixed as rapidly as possible, then introduced into the sample cell of the spectrophotometer (Beckman, model DU) to begin the series of readings. Four thermospacers adjoining the cell compartment were connected to a bath held at 25.00 ± 0.025° to maintain constant temperature during the reaction period. Time intervals were measured from the time of the initial reading.

The course of the reaction was followed by measurement of optical densities at an appropriate selected wave length, 280 mμ. First-order rate constants were calculated by means of the expression

$$k_1 = \frac{1}{t} \ln \frac{\mathrm{O.D.}_\infty - \mathrm{O.D.}_0}{\mathrm{O.D.}_\infty - \mathrm{O.D.}_t}$$

where $\mathrm{O.D.}_0$ is the optical density reading at the time of the initial reading (zero time), $\mathrm{O.D.}_t$ the reading at time t, and $\mathrm{O.D.}_\infty$ the reading after at least 15 half-lives. The initial optical density readings corresponded to 43 to 53% reaction with Ib and to 25 to 38% reaction with Ia. Measurements were made with both compounds until reaction was at least 90% complete. Over the range of the measurements the calculated first-order rate constants showed no regular trends. The results are summarized in Table III.

TABLE III

ELIMINATION RATES, 25°

Compound	10^4 [base], M	No. of values averaged	10^3 k_1, sec.$^{-1}$
Ib, *erythro* isomer	3.02	7	11.8 ± 0.4
	3.02	7	13.4 ± .7
	6.04	9	12.6 ± .9
	6.04	7	12.0 ± .6
Ia, *threo* isomer	3.02	10	3.64 ± .06
	3.02	12	3.63 ± .19
	3.02	11	3.82 ± .13
	6.04	8	3.39 ± .03
	6.04	9	3.19 ± .07

The average value of k_1 for Ib was (12.5 ± 0.6) × 10^{-3} sec.$^{-1}$, for Ia (3.53 ± 0.19) × 10^{-3} sec.$^{-1}$. Very few large deviations occurred among points in an individual run. The somewhat larger variations between values of k_1 for the duplicate runs may be due to temperature variation. The reactions were so fast that if slight temperature changes occurred during the mixing and solution transfer operations they would persist through most of the run. The necessity to work very fast doubtless also increased the chance for error in measuring times and optical densities. The unexpected slight decrease in reaction rate with increase in sodium hydroxide concentration may merely reflect inaccuracies in the measurements.

At the end of some of the runs ultraviolet spectra of the product solutions were determined over the range 230 to 320 mμ. These spectra agreed remarkably well with the spectrum of α-morpholino-*cis*-chalcone (Va). However, a slightly reduced absorption at *ca.* 260 mμ and increased absorption at wave lengths greater than 300 mμ suggested the formation of a few per cent. of a by-product with a spectrum resembling that of *trans*-chalcone.

Preliminary rate experiments conducted in a similar way with samples of the β-bromo-α-morpholino ketones IIIa and IIIb indicated slower elimination processes and a more complex kinetic behavior, with an increase in rate with increase in sodium hydroxide concentration. In 6.04 × 10^{-4} N sodium hydroxide, estimated initial pseudo-first-order rate constants at 25° were 0.7 × 10^{-3} sec.$^{-1}$ for IIIa and 1.5 × 10^{-3} sec.$^{-1}$ for IIIb. In the case of compound IIIb the ultraviolet spectrum of a solution at the end of the elimination reaction appeared to indicate the formation of about 60% of α-morpholino-*trans*-chalcone (Vb), 40% of α-morpholino-*cis*-chalcone (Va). The proportion of Vb formed appeared to be slightly higher from IIIa, although the spectrum of the product mixture was very similar.