exothermic reaction subsided, the white slurry was stirred and heated for an additional five minutes at 40–50°. In an attempt to obtain complete solution at this temperature, 6.8 g. of 37% formaldehyde was added to the mixture; no solution resulted. After stirring at the same temperature, for five minutes, the mixture was cooled, filtered and the product was air-dried overnight; 5.8 g. (77% yield), m.p. 143–144°. *Anal.* Calcd. for $C_6H_{14}O_6S_2$: C, 29.2; H, 5.72; S, 26.1. Found: C, 29.1; H, 5.59; S, 26.1.

This product was also obtained in an over-all yield of 70% by treating the reduction filtrate from 14-butanedisulfonyl chloride with formalin at a *p*H of 2-3, but our attempts to prepare the bis-(hydroxymethyl) sulfones from the corresponding 1,2-ethane-disulfonyl chloride,[15] 1,3-propanedisulfonyl chloride[16] and 1,5-pentanedisulfonyl chloride[17] in the same way were not successful.

1,4-Bis-(α-hydroxypropylsulfonyl)-butane.—To a stirred solution of 1.86 g. (0.01 mole) of 1,4-butanedisulfinic acid in 20 ml. of water was added 1.16 g. (0.02 mole) of propionaldehyde and the colorless precipitate which formed was diluted with 10 ml. of water. The precipitate was stirred for 15 minutes, collected, and washed successively with water, ethanol and ether. The product weighed 1.4 g., 46% yield, m.p. 117–120°; recrystallized from a mixture of 20 ml. of water and 10 ml. of propionaldehyde, m.p. 114–116°. *Anal.* Calcd. for $C_{10}H_{22}O_6S_2$: C, 39.8; H, 7.35. Found: C, 39.2; H, 7.20.

1,4-Bis-(acetoxymethylsulfonyl)-butane.—A mixture of 50 ml. of acetic anhydride and 9.84 g. (0.04 mole) of 1,4-bis-(hydroxymethylsulfonyl)-butane was heated on the steam-bath for 15 minutes with 10 drops of concentrated sulfuric. The solution was cooled to room temperature, chilled, filtered and the precipitate was washed with ether; 12.5 g., m.p. 104–113°. Recrystallization from ethyl acetate gave 9.4 g., 71.5% yield, m.p. 122–125°. *Anal.* Calcd. for $C_{10}H_{18}O_8S_2$: C, 36.35; H, 5.46; S, 19.4. Found: C, 36.35; H, 5.51, S, 19.4.

Preparation of 1,4-Bis-(N-substituted)-aminomethylsulfonyl-butanes.—The general procedure involved the addition of a methanolic solution of the amine or amide to a methanolic solution of 1,4-bis-(hydroxymethyl)-sulfonyl-butane. The reaction conditions are indicated in Table V.

BOUND BROOK, N. J.

(15) T. B. Johnson and J. M. Sprague, THIS JOURNAL, **58**, 1348 (1936).

(16) F. Asinger, F. Ebeneder and E. Böck, *Ber.*, **75B**, 42 (1942).

(17) P. W. Clutterbuck and J. B. Cohen, *J. Chem. Soc.*, 120 (1922).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CARNEGIE INSTITUTE OF TECHNOLOGY]

The Stereochemistry of Conjugate Additions. Convergent Configuration Control in Additions of Morpholine and N-Bromomorpholine to cis- and trans-α,β-Unsaturated Ketones

BY PHILIP L. SOUTHWICK AND RAYMOND J. SHOZDA[1]

RECEIVED MARCH 20, 1959

Addition of N-bromomorpholine yields the same α-bromo-β-morpholino-*p*-nitrobenzylacetophenone (form B) from either *cis*- or *trans*-4-nitrochalcone. This product is the diastereoisomer of the compound (form A) produced by adding morpholine to either *cis*- or *trans*-α-bromo-4-nitrochalcone. Likewise, 3-bromo-2-keto-4-morpholino-4-phenylbutyl benzoate was obtained in only one of the two possible configurations by addition of morpholine to the *cis*- or *trans*-3-bromo-2-keto-4-phenyl-3-butenyl benzoates. In the cases of the α-bromo-β-morpholinobenzylacetophenones and the α-bromo-β-morpholino-*p*-nitrobenzylacetophenones the diastereoisomer produced by the morpholine addition (form A) was converted by heating or by standing in solution into the apparently more stable diastereoisomer (form B), produced by N-bromomorpholine addition. The two diastereoisomeric α-bromo-β-morpholinobenzylacetophenones differ in their behavior when heated in methanol; form B undergoes solvolysis with rearrangement, but form A undergoes only rearrangement to give one of the β-bromo-α-morpholinobenzylacetophenones. These observations may indicate that form A has the *threo* configuration, form B the *erythro*. A mechanism involving protonation or bromination of a chelated enolic intermediate from the less hindered direction is advanced as a possible explanation of the observed convergent configuration control in these conjugate additions of morpholine and N-bromomorpholine.

In a previous investigation[2a] it was shown (see Chart I) that N-bromomorpholine adds to the olefinic bond of *trans*-chalcone (Ia) to yield chiefly the α-bromo-β-morpholinobenzylacetophenone (Va) (form B) which is the diastereoisomer of the compound (VIa) (form A) obtained by the addition of morpholine to the *cis* or *trans* forms (IVa or IIIa) of α-bromochalcone.[3,4] The present investigation represents an effort to discover the basis for the configuration control which has permitted these two conjugate addition reactions each to yield a different diastereoisomer. To this end, new experiments have been performed for the purpose of answering the following questions: (1) whether the configuration (*erythro* or *threo*) of an N-bromomorpholine adduct might be determined by the *cis* or *trans* configuration of the α,β-unsaturated ketone to which the addition occurred; (2) which of the diastereoisomeric adducts represents the thermally stable configuration; and (3) whether a comparison of reactivities might make it possible to establish *erythro* and *threo* configurations for the form A and form B adducts. The results of these experiments, which are described in the sections to follow, have delineated the major requirements for any theory which could account for the kind of configuration control peculiar to these conjugate additions.

Comparison of Additions to *cis* and *trans* Isomers.—It had been suggested that in the N-bromomorpholine addition to *trans*-chalcone the steric outcome might reflect some kind of concerted *trans* addition process.[2] This view of of the reaction implied that it might be possible to demonstrate that addition of N-bromomorpholine to a *cis*-α,β-unsaturated ketone would yield an addition product diastereoisomeric with that obtained from addition of N-bromomorpholine to the corresponding *trans* compound. This question has now

(1) National Science Foundation Fellow, 1956–1957. This paper is based on a thesis submitted by Raymond J. Shozda in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the Carnegie Institute of Technology, June, 1957.

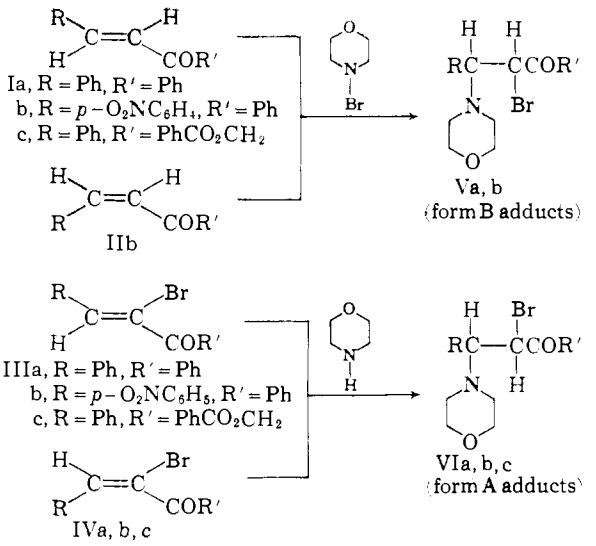
(2) (a) P. L. Southwick and W. L. Walsh, THIS JOURNAL, **77**, 405 (1955); (b) P. L. Southwick and D. R. Christman, *ibid.*, **75**, 629 (1953).

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

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

been investigated in experiments with the *cis* and *trans* forms of 4-nitrochalcone (IIb and Ib), both of which are solids of sufficiently high melting point to permit their purification by crystallization.

CHART I



Both of the isomers underwent addition of N-bromomorpholine at room temperature to yield α-bromo-β-morpholino-*p*-nitrobenzylacetophenone (Vb) in the same configuration (form B, m.p. 180°). The compound showed the oxidizing properties characteristic of an α-bromo ketone.[5] From *trans*-4-nitrochalcone the yield was essentially quantitative, and a yield of 74% was obtained from the *cis* isomer. Examination of the infrared spectra of the crude products failed to reveal the presence of any of the diastereoisomer (form A) melting at 126.5° (*vide infra*).

The addition of morpholine to the *cis* and *trans* forms (IVb and IIIb) of α-bromo-4-nitrochalcone also yielded but a single form of α-bromo-β-morpholino-*p*-nitrobenzylacetophenone (VIb). This product, however, was not the same as the adduct of N-bromomorpholine with the 4-nitrochalcones; it melted at 126.5° and has been designated form A. The infrared spectra of the crude adducts failed to reveal the presence of form B. The formation of the same adduct from both isomers of the α-bromo-α,β-unsaturated ketone parallels the results obtained by Jordan, Lutz and Hinkley[4] with *cis* and *trans* forms of α-bromochalcone (IVa and IIIa).

Although the same adduct was produced from both the *cis*- and *trans*-α-bromo-4-nitrochalcones, the addition was cleaner, more rapid, and produced a higher yield when conducted with the *trans* compound than with the *cis* compound. Whereas a yield of 77% was obtained from the *trans* isomer, a yield of only 21% was obtained from the *cis*, and in order to minimize the formation of colored by-products from reaction with latter compound it was necessary to interrupt the experiments before all of the starting material had reacted.[6]

(5) N. H. Cromwell and J. A. Caughlin, THIS JOURNAL, **67**, 2235 (1945), have demonstrated that α-bromo-β-amino ketones oxidize acidified iodide solutions, but that β-bromo-α-amino ketones do not.

(6) *Cf.* W. B. Black and R. E. Lutz, *ibid.*, **75**, 5990 (1953). It is pointed out by Black and Lutz that *cis* isomers frequently undergo conjugate additions less rapidly than do *trans* isomers.

A parallel series of experiments was also performed with a family of benzalacetone derivatives. Thus morpholine was found to add to both the *cis*- and the *trans*-3-bromo-4-phenyl-2-keto-3-butenyl benzoates (IVc and IIIc)[7] to produce the same form of 3-bromo-2-keto-4-morpholino-4-phenylbutyl benzoate (VIc). The yield was 68% from IIIc, 64% from IVc. Unfortunately, attempts to prepare the diastereoisomer of this compound by the addition of N-bromomorpholine to *trans*-4-phenyl-2-keto-3-butenyl benzoate (Ic) were unsuccessful; reaction occurred but no crystalline product could be isolated.

Thus in none of the experiments performed to date, either with morpholine or with N-bromomorpholine, did the original double bond configuration influence the configuration produced by the addition process; the configurations of the adducts were uniquely determined by the nature of the adding reagent. There was no evidence to support a concerted *trans* addition of N-bromomorpholine (or of morpholine) to the double bond. According to one possible interpretation, the outcome might be attributed to an initial rapid transformation under the influence of the adding reagent of the less stable *cis* unsaturated ketone into the more stable *trans* unsaturated ketone prior to the occurrence of the addition reaction, so that perhaps only additions to the *trans* isomer were in fact under observation in these experiments. The second possibility is that in both the morpholine and N-bromomorpholine additions an intermediate with only one asymmetric center is formed from both the *cis* and the *trans* isomers in the actual addition process. Since, as will be discussed below, it is likely that any isomerization of *cis*-α,β-unsaturated ketones which occurs in these experiments is brought about by reversible formation of the identical intermediate which is initially formed in the addition reactions,[7] the distinction between these two interpretations may in this instance be of no significance. Nevertheless, it should be noted that when allowed to stand for 5.5 days at −5° in a benzene solution containing N-bromomorpholine, *cis*-4-nitrochalcone was isomerized to the *trans* compound to the extent of 40% and no adduct was isolated. On the other hand, when reactions of morpholine with *cis*-α-bromo-4-nitrochalcone were interrupted short of completion, the recovered α-bromo-4-nitrochalcone was still in the form of the *cis* isomer.

Relative Stabilities of the Diastereoisomeric α-Bromo-β-morpholino Ketones.—In order to reach definite conclusions concerning the mechanism of the addition reactions in question it was necessary to know which of these additions, those involving morpholine or those involving N-bromomorpholine, were producing unstable diastereoisomers. The additions which produce such unstable adducts can be assumed to exert configuration control; *i.e.*, to lead to determination of configuration by providing a kinetic advantage for formation of the observed reaction product rather than by providing conditions which result in equilibration to produce the more stable configuration.

(7) P. L. Southwick and R. J. Shozda, *ibid.*, **81**, 3298 (1959). This paper and the references cited therein describe the preparation of the *cis* and *trans* unsaturated ketones used in the present work and conditions under which the *cis* and *trans* isomers are interconverted.

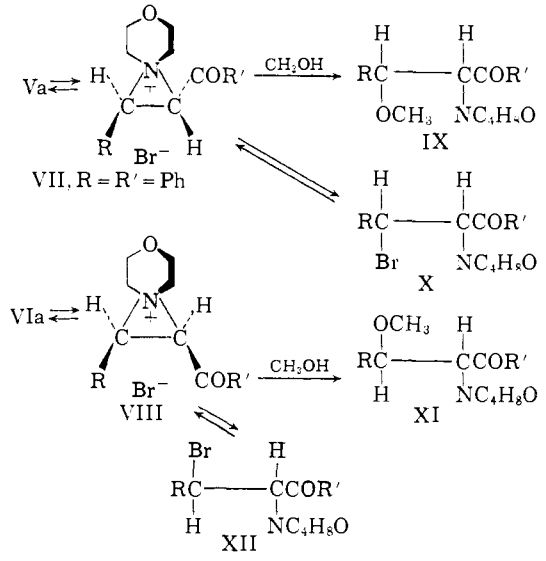
In the case of the adducts related to 4-nitrochalcone it could be shown that the isomer (form A) produced by the morpholine addition was, in fact, thermally less stable than the isomer (form B) produced by N-bromomorpholine addition. Form A of α-bromo-β-morpholino-4-nitrobenzylacetophenone (VIb) was converted into form B (Vb) when its benzene solution was refluxed for two hours, or merely allowed to stand at room temperature for forty-four hours. Heating of form A to its melting point also resulted in its conversion into form B. In the case of the α-bromo-β-morpholinobenzylacetophenones, conversion of form A (VIa) into form B (Va) was achieved only by heating form B in a nitrogen atmosphere to a temperature slightly above its melting point, and could not be carried to completion because of concomitant decomposition; there was little tendency for isomerization in benzene solution.

These observations indicate that in the morpholine additions which yield the form A adducts the configuration of the adducts is determined not by a stability relationship but by a kinetic advantage for the reaction path leading to form A. Since the reaction does not produce different configurations in the product from the two different geometrical isomers, it is not stereospecific in the same sense, as for example, is addition of halogen to simple olefins. However, since the single configuration produced is not the result of equilibration *after* the product has been formed, the addition process itself must determine the outcome by exerting what might be characterized as *convergent configuration control.* The convergence upon a single configuration in the product from stereoisomeric starting materials probably reflects (*vide infra*) a common intermediate with only a single asymmetric center. A very pronounced configuration control in the generation of the second asymmetric center in the last step of the reaction must then be required in order that only a single configuration be observed in the product.

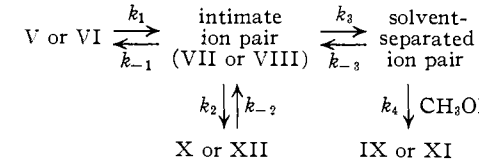
In the case of the N-bromomorpholine additions it is quite likely that both a kinetic advantage and a stability advantage combine to result in the production of the form B adducts. It is probable, although perhaps not certain, that the kinetic influence is the more important one, for it does not appear that form A adducts are rapidly converted into the more stable form B adducts under the conditions of the N-bromomorpholine additions. It was found that exposure to N-bromomorpholine in benzene solution at room temperature was without effect on VIa or VIb, even, in the case of the former compound, when prolonged to 85 hours.

Relationship of Solvolysis Behavior to Configuration.—In the previous investigation[2a] it had been found that α-bromo-β-morpholinobenzylacetophenone in form B (Va) undergoes solvolysis when heated with aqueous acetone to give the unstable compound β-hydroxy-α-morpholinobenzylacetophenone, and when heated with methanol to give a stable product which is evidently β-methoxy-α-morpholinobenzylacetophenone (IX or XI). The migration of the morpholino group indicated that neighboring group participation was involved in the solvolysis reactions, as in the reactions of similar compounds with amines which had been studied earlier by Cromwell and Cram.[8] Such participation would involve formation of an intermediate ion pair containing an ethylenimonium ion (VII or VIII).[8] Whichever form (A or B) has the *threo* configuration VI would be expected to give rise to an ion-pair with an ethylenimonium ion VIII having reduced stability due to the interaction of *cis*-phenyl and benzoyl groups, and it was considered likely that this effect might be made evident in a different solvolysis behavior for the two diastereoisomers.

An attempt to conduct the methanolysis of form A (VIa) of α-bromo-β-morpholinobenzylacetophenone under the same conditions used with form B did, indeed, reveal such a difference. Form A merely underwent rearrangement without solvolysis to give one of the forms of α-morpholino-β-bromobenzylacetophenone (X or XII). This product, which melted at 135–137°, differed from the two diastereoisomeric α-bromo-β-morpholinobenzylacetophenones (Va and VIa) in failing to oxidize acidified iodide solutions.[5]



The implication of these results with respect to the configurations of form A and form B are probably best discussed in terms of the analysis of the behavior of ion-pairs recently presented by Winstein and Robinson.[9] The transformations of these compounds in methanol which lead to the observed products can be formulated in the manner indicated by the equations



The reactions presumably pass through the stage of the "intimate ion-pairs" VII and VIII. Instability

(8) (a) N. H. Cromwell and D. J. Cram, THIS JOURNAL, **65**, 301 (1943); see also (b) N. H. Cromwell, G. V. Hudson, R. A. Wankel and P. J. Vanderhorst, *ibid.*, **75**, 5384 (1953); (c) F. H. Dickey, W. Fickett and H. J. Lucas, *ibid.*, **74**, 944 (1952); (d) G. K. Helmkamp and H. J. Lucas, *ibid.*, **74**, 951 (1952).

(9) S. Winstein and G. C. Robinson, *ibid.*, **80**, 169 (1958).

in the *cis*-ethylenimonium ion present in the intimate ion-pair VIII should cause ratios of reaction rate constants k_2/k_{-2} and k_2/k_3 for the *cis* ion-pair to exceed the corresponding ratios of rate constants for the more stable *trans* ion-pair VII.[9,10,11] The result should be to favor rearrangement as opposed to solvolysis more strongly for the *threo*-α-bromo-β-morpholino ketones VI than for the *erythro* compounds V. On this basis, therefore, it would be concluded that the form A adducts are of the *threo* configuration. To interpret the solvolysis results in the contrary manner would require the assumption that both the *cis* and *trans* ion-pairs reach the solvent separated stage (the more stable, *trans* ion-pair would presumably do so to a larger extent than the *cis* ion-pair) but that only the *cis*-ethylenimonium ion is sufficiently reactive toward methanol at the reflux temperature (*i.e.*, has large enough value for rate constant k_4) to undergo methanolysis to a significant extent, the *trans*-ethylenimonium ion undergoing "external ion-pair return" to VII and then to X instead. Such behavior for the *trans* ion might be observed in a solvolysis carried out in a solvent of low nucleophilicity, such as acetic acid, but it seems unlikely in methanol.[11,12] We therefore favor the view that the form A adducts have the *threo* configuration and the form B adducts the *erythro* configuration, but feel that more evidence must be sought before a final decision can be reached.

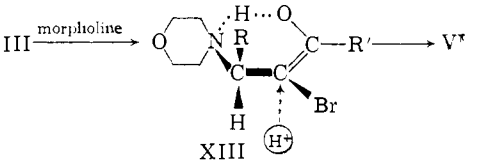
The other form A adducts, VIb and VIc, also yielded rearrangement products when heated in methanol, although the reactions were less clean-cut than with VIa. The form B adduct Vb, like Va, apparently underwent methanolysis, but attempts to isolate and characterize the methanolysis product from Vb were unsuccessful.

(10) Winstein and Robinson (ref. 9) have found that a change in substitution which should have the effect of stabilizing an ion of the phenonium bridged type results in a decrease in the extent of "internal return" from an "intimate ion pair" containing arylsulfonate as the other ion. In acetic acid it did not decrease the total extent of return to the covalent sulfonate as opposed to solvolysis, but it did so in ethanol. Apparently there were no large differences observed between *cis* and *trans* ions, but the steric interaction would have been only between methyl groups, not between groups comparable in size to the phenyl and benzoyl groups present in the structures under consideration here.

(11) The compressional strain between phenyl and benzoyl groups in the *cis*-ethylenimonium ion of VIII should be considerably greater than in the transition state leading from VIII to the rearranged bromo amino ketone XII. This effect should reduce the activation energy for the conversion VIII → XII; the value of k_2 should be increased by the steric interaction in VIII. There should be much less effect on activation energy due to steric effects in the conversion VII → X. Thus k_2 for VII → X should show no correspondingly enhanced value and should be smaller than k_2 for VIII → XII. On the other hand, the rate constant k_{-2} for the conversion X → VII should be larger than k_{-2} for XII → VIII, because of the greater steric interaction in the transition state (*cis* effect) in the latter reaction (see D. Y. Curtin, *Record Chem. Progress*, (*Kresge-Hooker Sci. Lib.*), **15**, 111 (1954)). There is probably no reason for assuming any great difference in the rate at which the ion-pairs VII and VIII would become solvent-separated.

(12) Some ethylenimonium ions have an appreciable stability, and the picrylsulfonates of several have been isolated. However, these ions hydrolyze readily in aqueous solutions and are destroyed very rapidly by hydroxide ions and other active nucleophilic agents. See (a) C. Golumbic, J. S. Fruton and M. Bergmann, *J. Org. Chem.*, **11**, 518 (1946); (b) J. S. Fruton and M. Bergmann, *ibid.*, **11**, 543 (1946); (c) P. D. Bartlett, S. D. Ross and C. G. Swain, THIS JOURNAL, **69**, 2971 (1947); (d) P. D. Bartlett, J. W. Davis, S. D. Ross and C. G. Swain, *ibid.*, **69**, 2977 (1947).

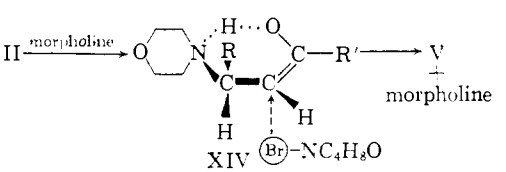
Discussion.—As we have seen, an explanation of the configuration control in these conjugate additions of morpholine and N-bromomorpholine probably must assume: (1) an intermediate of the same configuration from both *cis*- and *trans*-ketones, (2) addition processes which do not involve equilibration to the more stable diastereoisomer, and (3) production of *threo* configurations in the morpholine additions, *erythro* configurations in the N-bromomorpholine additions. By extension of suggestions offered in a previous paper of this series,[13] it is possible to accommodate these requirements. In the case of morpholine additions to α-bromo-α,β-unsaturated ketones the initial attack by morpholine would be pictured as leading to the chelated intermediate XIII suggested originally by Cromwell and Cram,[8] which might be expected to be ke-



XIII

tonized chiefly by protonation of the α-carbon from the less hindered side, the side of the β-hydrogen (the lower side as shown here). Recent work by Zimmerman has indicated that ketonizations within ordinary stable ring systems are controlled in this fashion.[14] The proton donor could be another molecule of XIII, or a morpholinium ion formed by a proton exchange between XIII and a morpholine molecule, etc. The result would be formation of an adduct of the *threo* configuration. The same intermediate XIII, and hence the same final product, would be formed from an α-bromo-α,β-unsaturated ketone of either the *cis* or the *trans* configuration. (Reversal of the initial addition could also result in isomerization of *cis*-ketones to *trans*-ketones during the addition process.)[7]

By modifying the mechanism outlined above only to the extent of substituting bromination for the concluding protonation step it is possible to formulate an explanation for the formation of *erythro* isomers by the addition of N-bromomorpholine to α,β-unsaturated ketones. In our solutions of N-bromomorpholine there is in all probability a trace of morpholine present. The initial reaction of this morpholine might be expected to yield the chelated intermediate XIV, which would then undergo



XIV

bromination by N-bromomorpholine on the less hindered side of the α-carbon to yield the *erythro* adducts V. The bromination would yield morpholine as the other reaction product and thus permit establishment of a chain reaction which would result in the net addition of the elements of N-bromo-

(13) P. L. Southwick and J. E. Anderson, *ibid.*, **79**, 6222 (1957).

(14) (a) H. E. Zimmerman, *ibid.*, **78**, 1168 (1956); (b) H. E. Zimmerman, *J. Org. Chem.*, **20**, 549 (1955).

morpholine, as observed. The additions of N-bromomorpholine are slow, as would be expected if the rate of the initial stage in the process were limited by the low concentration of morpholine present.

It may, of course, be possible to find alternative explanations for these results.[15] Further work will be required to test the various assumptions set forth here and, in particular, to establish with greater certainty the configurations of the isomeric adducts. A further investigation of the reactions of these adducts and their rearrangement products to provide further evidence on the question of configurations is in progress in these laboratories.

Experimental[16]

α-Bromo-β-morpholino-p-nitrobenzylacetophenone (Form A) (VIb). From *trans*-α-Bromo-4-nitrochalcone.—A solution of 2.66 g. (0.030 mole) of morpholine in 25 ml. of benzene was added in portions over a 4-hour period to a solution of 10 g. (0.030 mole) of *trans*-α-bromo-4-nitrochalcone[7] in 125 ml. of benzene. After the solution had stood at room temperature for another hour the solvent was removed under reduced pressure without heating. The residue was extracted with two separate portions of benzene. A trace of water-soluble material remained undissolved.

To the first benzene extract (75 ml. of solvent) was added 400 ml. of petroleum ether (b.p. 30–60°), and the mixture was cooled in a refrigerator until crystallization was completed. The 6.9 g. of yellow powder which separated from the solution was recrystallized by a similar procedure, using 125 ml. of benzene and 375 ml. of petroleum ether, to yield 6.0 g. of yellow needles, m.p. 123–126°. The second benzene extract (45 ml.) of the crude product yielded an additional 1.4 g. of adduct as yellow plates, m.p. 123–126°, when diluted with 200 ml. of petroleum ether and cooled.

The mother liquors from these crystallizations were combined and evaporated under reduced pressure without heating. Fractional crystallization of the residue from benzene and petroleum ether mixtures afforded 0.4 g. of product as yellow needles, m.p. 122–126°, and 2.4 g. of impure starting ketone, m.p. 60–75°. The total yield of adduct was 7.8 g. or 77% based on unrecovered starting material. Repeated crystallization of the adduct by dissolving it in benzene and diluting the solution with petroleum ether gave small white needles or plates, m.p. 125–126.5° (from 115°).[17] Because of partial conversion to form B during melting, higher melting points were sometimes obtained, and samples originally of form A remelted at *ca.* 145–160°.

Anal. Calcd. for $C_{19}H_{19}O_4N_2Br$: C, 54.42; H, 4.57; N, 6.68. Found: C, 54.54; H, 4.58; N, 6.59.

The compound liberated 82% of the theoretical amount of iodine from an acidified solution of potassium iodide.[5]

The most prominent bands of the infrared spectrum (30 mg./ml. in chloroform) were at 5.92s, 6.25, 6.55s, 6.90, 7.41s, 7.90, 8.97s, 10.13, 11.38s and 11.68μ (strongest bands (less than 40% transmittance) are marked with the letter s).

From *cis*-α-Bromo-4-nitrochalcone.—A solution of 1.5 g. (0.0045 mole) of the *cis* isomer,[7] 0.39 g. (0.0045 mole) of morpholine and 25 ml. of benzene was allowed to stand at room temperature for 11.5 hours. The dark solution, from which a small amount of water-soluble solid had separated, was diluted with 25 ml. of ether and washed thoroughly with water, the first portion of which was acidified with dilute hydrochloric acid. The solution was dried over magnesium sulfate and evaporated under reduced pressure without heating to give 1.4 g. of a yellow residue which did not completely solidify. The material was dissolved in 10 ml. of benzene, 100 ml. of petroleum ether (b.p. 30–60°) was added, and the solution was cooled. The 0.8 g. of yellow needles, m.p. 110–117°, which separated had an infrared spectrum which corresponded to a mixture of the form A adduct and the starting ketone.[7] Recrystallization from 8 ml. of benzene and 100 ml. of petroleum ether gave 0.4 g. (21%) of a product melting at 118–124° and having the infrared spectrum of the form A adduct.

Neither the crude adduct from the *cis*-ketone nor from the *trans*-ketone showed any indication of infrared bands characteristic of the form B adduct.

α-Bromo-β-morpholino-p-nitrobenzylacetophenone (Form B) (Vb). From *trans*-4-Nitrochalcone.—A solution of N-bromomorpholine[2] was prepared by adding a solution of 11.1 g. (0.127 mole) of morpholine in 15 ml. of benzene to a stirred solution of 9.7 g. (0.0606 mole) of bromine in 60 ml. of benzene. The precipitated morpholine hydrobromide (10.2 g; 100%) was removed by filtration and washed with 50 ml. of benzene, which was added to the filtered solution of N-bromomorpholine.

The N-bromomorpholine solution was added to a solution of 5.0 g. (0.0198 mole) of *trans*-4-nitrochalcone[7] in 350 ml. of benzene. After the mixture had been kept at room temperature for 12 hours, it was diluted with 500 ml. of petroleum ether (b.p. 30–60°) and cooled in a refrigerator until crystallization was complete. The crop of yellow crystals of the adduct (2.7 g.) which was filtered from the mixture melted at 161–168° (from 150°). The filtrate was evaporated to dryness under reduced pressure without heating and the yellow residual solid (5.7 g.; total crude yield of adduct 8.4 g., 100%) was extracted with 60 ml. of cold benzene. The undissolved residue was crystallized from hot benzene to give 2.4 g. of yellow crystals, m.p. 175–178.5° (from 160°), and the cold benzene extract yielded an additional 1 g. of material, m.p. 156–163° (from 150°), when diluted with 200 ml. of petroleum ether (b.p. 30–60°). Repeated recrystallization of the various fractions of crude product from benzene yielded yellow granular crystals, m.p. 178.5–180° (from 160°).

Anal. Calcd. for $C_{19}H_{19}O_4N_2Br$; C, 54.42; H, 4.57; N, 6.68. Found: C, 54.84; H, 4.49; N, 6.61.

The compound liberated 95.5% of the theoretical amount of iodine from an acidified solution of potassium iodide.

The most prominent bands of the infrared spectrum (30 mg./ml. in chloroform) were at 5.94s, 6.23, 6.54s, 6.89, 7.40s, 7.90, 8.97s, 9.95, and 11.68μ (strongest bands (less than 50% transmittance) are marked with the letter s).

From *cis*-4-Nitrochalcone.—Three grams (0.012 mole) of *cis*-4-nitrochalcone[7] was dissolved in a solution of 0.0354 mole of N-bromomorpholine in 61 ml. of benzene which had been prepared as described above. Filtration of the solution after 10 hours at room temperature removed 1.4 g. of a solid, m.p. 171–175° (from 160°). When the filtrate was diluted with 300 ml. of petroleum ether and cooled, another 2.3 g. of product, m.p. 174–176°, separated, raising the total yield to 3.7 g. (74%). An additional 0.9 g. of less pure product (m.p. *ca.* 147°) was obtained by evaporation of the mother liquor.

These materials gave the infrared spectrum of the form B isomer, as described above. Bands characteristic of the form A isomer were absent from crude adducts from both the *cis*- and *trans*-4-nitrochalcones.

In a similar experiment in which 3 g. of *cis*-4-nitrochalcone was treated with 0.012 mole of N-bromomorpholine at −5° for 5.5 days, 1.7 g. (57%) of starting material, m.p. 88–90°, was recovered and 1.2 g. (40%) of crude *trans*-4-nitrochalcone, m.p. 140–152°, was the only other product isolated.

3-Bromo-2-keto-4-morpholino-4-phenylbutyl Benzoate (Form A) (VIc). From *trans*-3-Bromo-2-keto-4-phenyl-3-butenyl Benzoate (IIIc).[7]—An absolute ether solution (2.61 ml.) containing 0.0522 g. (0.0006 mole) of morpholine was

(15) N. H. Cromwell, THIS JOURNAL, **81**, 4702 (1959), has proposed a new theory to account for the effects of variations in sizes of substituent groups on steric controls operating in conjugate additions of primary amines or N-halogen primary amines which lead ultimately to the formation of ethylenimine ketones. The new theory differs from the one we have favored (ref. 13) in assuming that the conformation of the intermediate enol is controlled not by chelation but by steric interactions of substituents. Its application to the additions described here would require a knowledge of the comparative effective sizes of the phenyl and morpholino groups.

(16) Melting points are corrected. Microanalyses by Drs. G. Weiler and F. B. Strauss, Oxford, England, and Geller Microanalytical Laboratories, Bardonia, N. Y. Infrared spectra were determined with a Perkin–Elmer model 21 spectrophotometer.

(17) Many of the compounds described in this paper melted with decomposition (or isomerization). To get reproducible melting point values on each compound it was necessary to begin the heating of the capillary tube in each determination with the melting-point block at the same temperature, and to maintain the same rate of heating, which was 5°/min. for all of the samples described. The temperature at which the sample was inserted in the block is recorded in parentheses after many of the melting points as, for example (from 115°).

added to a solution of 206 mg. (0.0006 mole) of the *trans* unsaturated ketone in 25 ml. of absolute ether. After the mixture had been cooled in a refrigerator overnight, the white solid product which had separated was removed by filtration, washed with ether and then water, and dried. This material, which melted at *ca.* 105°, did not differ appreciably in infrared spectrum from fully purified product. The yield was 177 mg. (68.6%). Evaporation of the filtrate from the reaction mixture yielded 85 mg. of oil. The solid product was purified by recrystallization from benzene–petroleum ether (b.p. 30–60°) mixtures to yield fine, white needles, m.p. 128–130° (from 115°).

Anal. Calcd. for $C_{21}H_{22}O_4NBr$: C, 58.34; H, 5.13; N, 3.24. Found: C, 58.44; H, 5.23; N, 3.13.

The compound liberated 41.4% of the theoretical amount of iodine from an acidified solution of potassium iodide.[5]

Prominent discrete bands of the infrared spectrum (30 mg./ml. in chloroform) were at 5.79s, 6.88, 7.87s (broad base, two shoulders beyond 8), 8.97s and 9.35μ (strongest bands (less than 50% transmittance) marked s).

From *cis*-3-Bromo-2-keto-4-phenyl-3-butenyl Benzoate (IVc).[7]—An absolute ether solution (2.52 ml). containing 0.0505 g. (0.00058 mole) of morpholine was added to 201 mg. (0.00058 mole) of the *cis* unsaturated ketone in 25 ml. of absolute ether. A procedure identical with that described above afforded 162 mg. (64.5%) of a white solid, m.p. 102–106° (from 92°), and 75 mg. of oil. The infrared spectrum of the crude solid was indistinguishable from that of the pure sample of the form A adduct.

Thermal Isomerization of Form A Adducts to Form B Adducts. Isomerization of α-Bromo-β-morpholino-p-nitrobenzylacetophenone (Form A) (VIb).—A solution of 38 mg. of the adduct (m.p. 125–126.5°) in 5 ml. of benzene was allowed to stand at room temperature for 44 hours. The solution was evaporated under reduced pressure at room temperature. The residue was dissolved in 1 ml. of benzene, and 20 ml. of petroleum ether (b.p. 30–60°) was added to the solution. A yellow granular solid (24 mg.) crystallized when the solution was cooled. This proved to be a crude sample of the form B adduct, m.p. 165° dec. (from 110°) with some softening at 117°.

A solution of 0.3 g. of the form A adduct (m.p. 125–126.5°) in 10 ml. of benzene was refluxed for 2 hours. The colorless solution became pale-yellow during the heating period. The residue obtained when the solvent was removed under reduced pressure melted at 171–177° dec. (from 150°); it represented the form B adduct in nearly pure form.

A 0.3-g. sample of the form A adduct, m.p. 125–126.5°, was kept at a temperature of 125–135° for 10 minutes in a small flask in which a nitrogen atmosphere was maintained. The material resolidified completely and showed a melting point of 162–165° (from 147°). Crystallization from benzene yielded essentially pure form B adduct Vb as yellow granules, m.p. 177–179° dec. (from 160°).

Isomerization of α-Bromo-β-morpholinobenzylacetophenone (Form A) (VIa).—The compound was not changed by heating in benzene as in the second experiment described above. However, when a 1-g. sample was heated for 2 minutes in the dry state under a nitrogen atmosphere, as in the third experiment, the sample darkened and yielded a tarry mixture, which was extracted with 25 ml. of boiling petroleum ether (b.p. 65–110°). The extract was decanted from an insoluble, tarry residue and cooled. The 0.6 g. of light-yellow solid which separated yielded 139 mg. of the form B adduct as yellow prisms, m.p. 135–137° (from 120°), when crystallized from petroleum ether (b.p. 65–110°). Some form A adduct was also present, and this separated as white needles after crystallization of the form B adduct was nearly complete.

Attempts to Equilibrate Form A and Form B Adducts in the Presence of N-Bromomorpholine or Morpholine. Experiments with N-Bromomorpholine Solutions.—The form A adducts VIa and VIb were dissolved in benzene solutions of N-bromomorpholine such as were used in the preparation of the form B adducts. From 1 g. (0.0024 mole) of VIb kept at room temperature for 9.5 hours in 20 ml. of benzene containing 0.012 mole of N-bromo-morpholine, 0.7 g. of crude starting material melting in the range 106–114° (from 100°) was recovered. Recrystallization yielded only the form A adduct, 0.5 g., m.p. 117–124° (from 110°). Similarly, from 0.5 g. of VIa kept at room temperature for 85 hours in 5 ml. of a benzene solution containing 0.003 mole of N-bromomorpholine, 0.3 g. of pure starting material, m.p. 126.5–129° (from 120°), was recovered.

Experiments with Morpholine Solutions.—The form A adduct VIb (1 g.) yielded only a small amount (32 mg.) of morpholine hydrobromide when kept in solution for 13.5 hours at room temperature with 0.42 g. of morpholine in 20 ml. of benzene. Half of the starting material was recovered largely in the original configuration, m.p. 131–134° (from 115°, melted sample remelted at 155–165°). The only other product found was an amorphous solid (0.2 g.), m.p. 50–85°.

The form B adduct Vb (1.0 g.) likewise yielded only a trace of morpholine hydrobromide when kept for 12 hours in a solution of 0.42 g. of morpholine in 65 ml. of benzene. Following separation and purification, 0.8 g. of the starting form B adduct, m.p. 176–177° (from 160°), was recovered unchanged.

Rearrangements of the Form A Adducts Upon Heating in Methanol. Preparation of β-Bromo-α-morpholinobenzylacetophenone from VIa.—A solution of 2.0 g. of the form A adduct VIa[2-4] in 25 ml. of absolute methanol was heated on a steam-cone for 20 minutes. An aqueous sodium bicarbonate solution was added to the mixture. The 1.7 g. of solid which separated was recrystallized several times from petroleum ether to yield small, pale-yellow needles, m.p. 135–137° (from 120°).

Anal. Calcd. for $C_{19}H_{20}O_2NBr$: C, 60.97; H, 5.39; N, 3.74. Found: C, 61.34; H, 5.37; N, 3.62.

Qualitative analysis demonstrated the presence of bromine, but the compound did not oxidize an acidified solution of potassium iodide. The melting point of a mixture of the product and the starting material (m.p. 130–133°) was depressed to 127–132°. The form B adduct Va had yielded the methanolysis product IX in 77% yield when heated for 20 minutes in methanol; see ref. 2a.

Preparation of β-Bromo-α-morpholino-p-nitrobenzylacetophenone from VIb.—A solution of 1.5 g. of the form A adduct VIb in 25 ml. of absolute methanol was heated on a steam-cone for 30 minutes. The solvent was removed under reduced pressure and the residue was extracted with ether. The insoluble portion was converted to an ether-soluble material when treated with aqueous sodium bicarbonate; 0.18 g. of an oily solid was isolated, but could not be purified.

The residue from evaporation of the ether extract was extracted with hot petroleum ether (b.p. 65–110°). A portion remained undissolved. When cooled, the petroleum ether extract deposited 0.22 g. of solid (fraction I). The melting point of fraction I depended upon the heating procedure. When a sample was placed in a melting-point block at 100° and the temperature was raised slowly, decomposition occurred at 157–163°. When placed in a block at 155° the material quickly melted and then resolidified; raising the temperature at 5°/min. then caused it to remelt with decomposition at 165–169°. An additional quantity of similar material was obtained by treating the petroleum ether-insoluble fraction mentioned above with aqueous sodium bicarbonate and then extracting with ether. Except for a small amount of unidentified solid (0.06 g., m.p. 165–168°), the material dissolved, and yielded 0.35 g. of yellow crystals (fraction II) following evaporation of the ether and recrystallization of the residue from petroleum ether. The melting point behavior of fractions I and II was the same, and the two were combined for a final purification by several recrystallizations from petroleum ether (b.p. 65–110°). Light-yellow needles were obtained which melted immediately when placed in a melting point block at 155°, then resolidified and decomposed at 170–172° when the temperature rise was 5°/min.

Anal. Calcd. for $C_{19}H_{19}O_4N_2Br$: C, 54.42; H, 4.57; N, 6.68. Found: C, 54.27; H, 4.38; N, 6.57.

Qualitative analysis demonstrated the presence of bromine, but the compound did not oxidize potassium iodide in acid solution.[5]

Preparation of 4-Bromo-2-keto-3-morpholino-4-phenylbutyl Benzoate from VIc.—A solution of 0.35 g. of the adduct VIc in 20 ml. of absolute methanol was heated on a steam-cone for 20 minutes. The cooled solution was poured into an aqueous sodium bicarbonate solution, and the mixture was extracted with ether. The ether extract was washed with water, dried, and evaporated. The slightly tacky residue was crystallized from petroleum ether (b.p. 65–110°) to give 0.18 g. of product, m.p. 106–107° dec. Following sev-

eral recrystallizations from petroleum ether, fine white needles were obtained, m.p. 128.5–130.5° (from 100°).

Anal. Calcd. for $C_{21}H_{22}O_4NBr$: C, 58.34; H, 5.13; N, 3.24. Found: C, 57.62; H, 5.08; N, 3.20.

Qualitative analysis indicated the presence of bromine, but the compound did not immediately oxidize potassium iodide in aqueous solution, as did the starting material.

Methanolysis of α-Bromo-β-morpholino-p-nitrobenzylacetophenone (Form B) (Vb).—A solution of 4.0 g. of the adduct Vb in 100 ml. of methanol was refluxed for 2.5 hours. After removal of the solvent under reduced pressure, there was left 3.8 g. of light-yellow granules. The residue was readily soluble in methanol and methanolic ether, but was insoluble in ether, petroleum ether, and benzene; it did not oxidize an acidified solution of potassium iodide. Upon insertion in a block preheated to 170°, a sample appeared to evolve a gas; raising the temperature caused decomposition at 178–183°.

The product was treated with sodium bicarbonate and extracted with ether. The ether extract was washed with water, dried over magnesium sulfate, and evaporated to give a glassy solid which melted immediately when immersed in a block heated to 60°. Crystallization from petroleum ether (b.p. 65–110°) gave crops of solid, melting over wide ranges between the limits of 78–153°, which consisted of small yellow granules about which were clustered fine yellow needles. No homogeneous material could be isolated. Qualitative analysis of fractions melting at 117–153° and 78–118° indicated the presence of nitrogen and a small amount of halogen.

Acknowledgment.—We are indebted to Dr. Allan K. Colter for helpful comment in connection with the discussion of the solvolysis and rearrangement reactions.

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[CONTRIBUTION FROM THE MERCK, SHARP AND DOHME RESEARCH LABORATORIES, DIVISION OF MERCK AND CO., INC.]

The Synthesis of 2-(6-Hydroxy-2-methoxy-3,4-methylenedioxyphenyl)-benzofuran, A New Compound from Yeast

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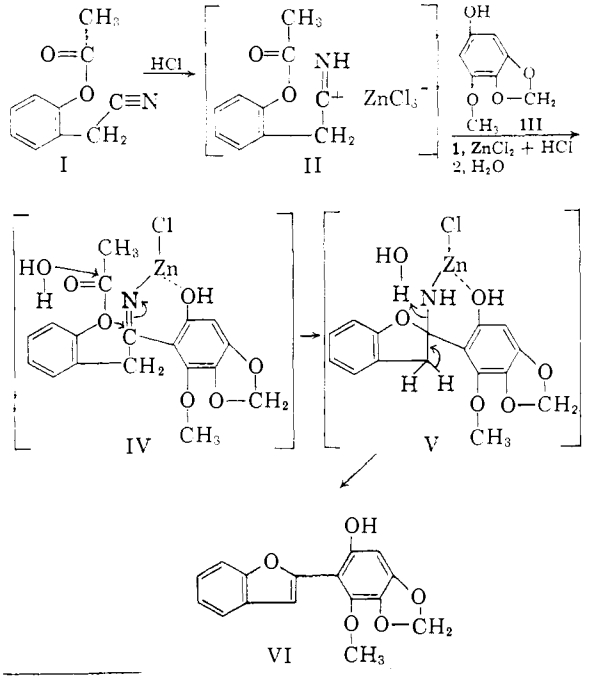
RECEIVED MAY 11, 1959

2-(6-Hydroxy-2-methoxy-3,4-methylenedioxyphenyl)-benzofuran (VI), was synthesized by the condensation of *o*-acetoxyphenylacetonitrile (I) with 3-methoxy-4,5-methylenedioxyphenol (III). The deoxy-analog, 2-(2-methoxy-3,4-methylenedioxyphenyl)-benzofuran (XIV), was synthesized from methyl *o*-benzyloxyphenylacetate (IX) and methyl 2-methoxy-3,4-methylenedioxybenzoate (X). Nitration of the deoxy-analog XIV gave 2-(2-methoxy-3,4-methylenedioxyphenyl)-3-nitrobenzofuran (XV).

Forbes, Zilliken, Roberts and György[1] isolated and characterized a new crystalline compound from yeast which *in vitro* protects the red blood cells of vitamin E deficient rats from hemolysis by dialuric acid. From a series of degradation studies[2] this compound was shown to be 2-(6-hydroxy-2-methoxy-3,4-methylenedioxyphenyl)-benzofuran (VI).



We now describe the synthesis of VI and its 6-deoxy analog, 2-(2-methoxy-3,4-methylenedioxyphenyl)-benzofuran (XIV).

2-(6-Hydroxy-2-methoxy-3,4-methylenedioxyphenyl)-benzofuran (VI) was synthesized in about 10% yield by the condensation of *o*-acetoxyphenylacetonitrile (I) with 3-methoxy-4,5-methylenedioxyphenol[3] (III) under the conditions of the Hoesch synthesis.[4] *o*-Acetoxyphenylacetonitrile was converted *in situ* to the intermediate II which in turn condensed with 3-methoxy-4,5-methylenedioxyphenol in ether solution in the presence of anhydrous zinc chloride and hydrogen chloride. After several days, an aqueous extract of the reaction mixture was heated yielding a mixture of products from which *o*-hydroxyphenylacetic acid and 2-(6-hydroxy-2-methoxy-3,4-methylenedioxyphenyl)-benzofuran (VI) were isolated. The isolation of the benzofuran derivative at this stage of the reaction sequence would not be predicted in view of the relatively drastic conditions necessary to cyclize the related derritols[5,6] and especially in the light of the well-documented studies of Whalley and Lloyd[7] with hydroxy-deoxybenzoins. They demonstrated the spontaneous cyclization of 2′-hydroxy-deoxybenzoins to benzofurans, but in contrast encountered an increased stability in the

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