$$E_a = \frac{2.303RT_1T_2}{T_2 - T_1} \log k_2/k_1$$

Entropies of activation were calculated from the equation

$$\Delta S^{\ddagger}_{T_1} = \frac{(E_a - RT_1) + 2.303RT_1\left(\log \frac{k_{rate}h}{kT_1}\right)}{T_1}$$

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EVANSTON, ILL.

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

The Stereochemistry of Conjugate Additions. The Methanol Solvent Effect on Configuration Control in Additions of Amines, N-Bromoamines and Iodine–Amine Complexes[1]

BY PHILIP L. SOUTHWICK AND RAYMOND J. SHOZDA[2]

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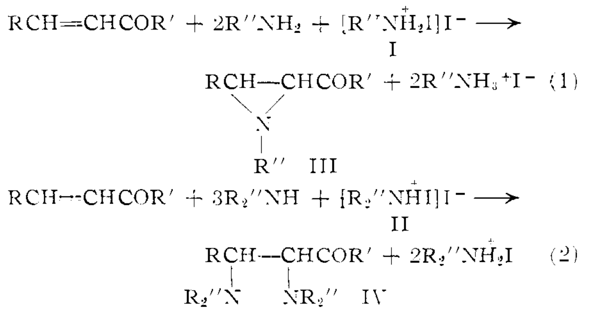
When ethylenimine ketones are formed by the action of primary amines and iodine–primary amine complexes or N-bromo primary amines on chalcones, or by the action of primary amines on α-bromochalcones, the nature of the solvent may have a decisive influence upon the determination of the configuration of the product. Substitution of methanol for benzene as the solvent in the reaction increased greatly the proportion of *trans*-ethylenimine ketone formed in reactions of *trans*-chalcone or *trans*-4-nitrochalcone with cyclohexylamine and the iodine–cyclohexylamine complex or N-bromocyclohexylamine. On the other hand, substitution of methanol for benzene in reactions of cyclohexylamine with *trans*-α-bromochalcone or *trans*-α-bromo-4-nitrochalcone greatly increased the proportion of *cis*-ethylenimine ketone obtained. It was not possible to demonstrate a difference in the isomeric composition of the ethylenimine ketone product obtained from *cis*-4-nitrochalcone as compared with *trans*-4-nitrochalcone in reactions with cyclohexylamine and the iodine–cyclohexylamine complex. An electronic effect of the nitro group is made evident in a change in the *cis–trans* isomer ratios observed in the ethylenimine ketones obtained from *trans*-4-nitrochalcone and *trans*-α-bromo-4-nitrochalcone as compared with those obtained by the same reactions from *trans*-chalcone and *trans*-α-bromochalcone. The observed solvent and electronic effects are discussed in terms of the hypothesis that under suitable conditions configuration control is determined by asymmetric steric hindrance to protonation or halogenation of intermediate chelated amino enols.

When an α,β-unsaturated ketone is treated with iodine and an excess of a primary or secondary amine, the olefinic bond of the unsaturated ketone may undergo attack by the amine and the iodine–amine complex (I or II) with the formation of an ethylenimine ketone (III) or an α,β-diamino ketone



(IV). In the original papers[3] on these reactions it was pointed out that a relatively high degree of configuration control seemed evident. For example, in reactions of the benzylamine and cyclohexylamine–iodine reagents with chalcone, only the *trans*-ethylenimine ketone was isolated.[3] Moreover, in the case of a number of other α,β-unsaturated ketones examined more recently by Cromwell and his associates,[4] only the *trans*-ethylenimine ketones were found to result from the iodine–amine additions, even when efficient chromatographic methods were applied in the effort to separate any *cis* isomer which might have been formed. The basis of such configuration control has been the subject of conjecture,[5,6] but more information is needed to establish the correct explanation.

The purpose of the present investigation was threefold. It was desired first to establish whether or not the iodine–amine additions were stereospecific in the same sense as halogen additions to simple olefins, and hence capable of yielding products having different configurations (or ratios of configurations) when applied to a *cis*-unsaturated ketone as opposed to a *trans*-unsaturated ketone. It was also considered of interest to test the hypothesis[5] that intermediate chelated amino enols play a part in the configuration control observed in these reactions by the expedient of introducing an electronic effect which might influence the stability of the assumed chelate ring. Finally, since several details of procedure had been varied in the original investigation without determining quantitatively the effects of such variation on the proportion of diastereoisomers formed, it was desired to examine in more detail one of the addition reactions reported in the first paper. This last line of investigation disclosed a pronounced solvent effect on configuration control in the reactions of chalcones with the

(1) For the previous paper in this series see P. L. Southwick and R. J. Shozda, THIS JOURNAL, **81**, 5435 (1959).

(2) National Science Foundation Fellow, 1956–1957. This paper is abstracted from 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.

(3) (a) P. L. Southwick and D. R. Christman, THIS JOURNAL, **74**, 1886 (1952); (b) **75**, 629 (1953).

(4) (a) N. H. Cromwell, R. P. Cahoy, W. E. Franklin and G. D. Mercer, *ibid.*, **79**, 922 (1957); (b) N. H. Cromwell and R. J. Mohrbacher, *ibid.*, **75**, 6252 (1953).

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

(6) See (a) N. H. Cromwell, *ibid.*, **81**, 4702 (1959), and (b) H. E. Zimmerman and W. H. Chang, *ibid.*, **81**, 3634 (1959). These investigators have arrived independently at theories which provide a similar basis for predicting the configurational outcome in ketonizations of unchelated acyclic enols. Cromwell directs his attention mainly to the types of reactions under consideration here, and they are also discussed by Zimmerman.

TABLE I

FORMATION OF ETHYLENIMINE KETONES BY THE REACTION OF α,β-UNSATURATED KETONES WITH IODINE OR BROMINE AND CYCLOHEXYLAMINE AT 28°

Expt.	Solvent	Added substance[a]	Other reactants[a]	Reaction time, hrs.:min.	Yield, %	ΔD[b]	% *trans*-ethylenimine
1	Benzene	4 C	*t*-Ch + I_2	2:40	97	0.154	66
2	Benzene	I_2	*t*-Ch + 4 C	2:00	100	.126	64
3	Benzene	I_2	*t*-Ch + 12.5 C	5:20	98	.108	61
4	Methanol	I_2	*t*-Ch + 4 C	1:30	100	.301	88
5[c]	Benzene	I_2	*t*-4NCh + 4 C	3:00	90	.060	52
6[c]	Benzene	I_2	*c*-4NCh + 4 C	5:10	63[e]	.053	51
7[c]	Methanol	I_2	*t*-4NCh + 4 C[d]	4:00	90	.189	73
8	Benzene	Br_2	*t*-Ch + 4 C	9:15	10[f]	...	0[g]
9	Methanol	Br_2	*t*-Ch + 4 C	8:15	60[f]	...	73[g]
10	Benzene	Br_2	*t*-4NCh + 4 C	3:30	85[f]	.003	43
11	Methanol	Br_2	*t*-4NCh + 4 C	3:40	60[f]	.101	58

[a] C = cyclohexylamine, *t*-Ch = *trans*-chalcone, *t*-4NCh = *trans*-4-nitrochalcone, *c*-4NCh = *cis*-4-nitrochalcone; coefficients refer to moles of reactants per mole of ketone. [b] Calculated from the infrared spectrum of the mixture; $D_{5.98} - D_{5.90 \text{ or } 5.91}$ (see Experimental section). [c] Performed at 28° without the thermostated bath. [d] Initially a slurry. [e] The yield of cyclohexylamine hydroiodide was 67%. [f] Remaining material accounted for as starting ketone. [g] Estimated by infrared spectroscopic comparison with compounded mixtures containing starting material.

primary amine–iodine combination or the primary amine–N-bromoamine combination. These results prompted us to perform a set of exploratory experiments by which it was revealed that the same change of solvent produced the opposite effect upon the ratio of *cis* to *trans* isomers when the same ethylenimine ketones were prepared by the most important alternative method, the reaction of primary amines with α-bromochalcones.[7]

trans-Chalcone and the *cis*- and *trans*-4-nitrochalcones were the unsaturated ketones selected for study. The iodine–amine reagent employed was the iodine–cyclohexylamine complex[3]; it was chosen because it has been used in the previous work with *trans*-chalcone and because it was expected that the configurations of the new ethylenimine ketones to be obtained from the 4-nitrochalcones could be determined by use of methods established by Cromwell and his associates.[8] An analytical method based upon infrared correlations developed by these workers was, in fact, found to be suitable for our purposes.

Table I records the results of the experiments performed with the iodine–cyclohexylamine complex. Except as otherwise indicated, all were conducted in a constant-temperature bath at 28°. In addition to variations in the substitution and configuration of the starting ketone, effects of changing the order of addition of reactants and of changing the solvent from benzene to methanol are shown. Benzene and methanol had both been used in the previous work,[3] but no critical examination of possible solvent effects had been made.

In experiments 1, 2, and 3 the iodine–cyclohexylamine reaction was conducted on *trans*-chalcone in benzene solution. In experiment 1 cyclohexylamine was added to a mixture of *trans*-chalcone and iodine, whereas in experiments 2 and 3 iodine was added to a mixture of *trans*-chalcone and cyclohexylamine. In experiments 2 and 3, particularly in the latter, the reaction occurred in a solution made distinctly basic by unchanged amine. It will be observed, however, that the effect of this alteration on yields and isomer ratios was very slight. It is also apparent that the degree of configuration control reflected by the 61–66% content of *trans* isomer in the ethylenimine ketone product mixtures is not as high as had been assumed previously[3] on the basis of the relative ease of isolating and purifying the *trans* product. The yield of mixed isomeric ethylenimine ketones was very high.

Experiments 5 and 6 were performed to test the possibility that the configuration of the α,β-unsaturated ketone would influence the configuration ratio in the ethylenimine product mixture. The entries in Table I record the failure of these experiments to demonstrate any such effect; *trans*-4-nitrochalcone afforded an ethylenimine mixture containing 52% of the *trans* isomer, while *cis*-4-nitrochalcone, although reacting more slowly, produced a product whose isomer composition (51% *trans*) was not significantly different. Thus, there was no evidence of the preservation of a configurational difference during the reaction process. It is possible that isomerization of the *cis* isomer of the unsaturated ketone to the *trans* isomer may have occurred so rapidly as to largely precede the addition reaction,[9] and hence conceivable that a significant difference might have been detected if the *cis* isomer had been more resistant to isomerization. Moreover, the fact that the isomer ratio in the product was so close to unity in these experiments might indicate that the *cis*- and *trans*-4-nitrochalcones did not represent a good choice of starting materials for demonstrating the steric effect in question. However, the demonstration of convergent configuration control[10] in the related additions of N-bromomorpholine to the *cis*- and *trans*-4-ni-

(7) For a recent review of the chemistry of ethylenimine ketones see N. H. Cromwell, *Record Chem. Progress (Kresge Hooker Sci. Lib.)*, **19**, 215 (1958).

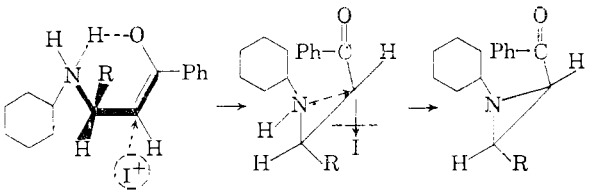
(8) (a) N. H. Cromwell, N. G. Barker, R. A. Wankel, P. J. Vanderhorst, F. W. Olson and J. H. Anglin, Jr., THIS JOURNAL, **75**, 1044 (1951); (b) N. H. Cromwell and M. A. Graff, *J. Org. Chem.*, **17**, 414 (1952).

(9) *cis*-4-Nitrochalcone is to a large extent isomerized to the *trans*-form when allowed to stand for periods of 1–2 hours in dilute acetone or benzene solutions containing an equal weight of iodine or an excess of cyclohexylamine; see P. L. Southwick and R. J. Shozda, THIS JOURNAL, **81**, 3298 (1959).

(10) See ref. 1. It was suggested that the term *convergent configuration control* be applied when different stereoisomers yield a product of the same configuration (or ratio of configurations) by any process not involving equilibration of stereoisomers of the ultimate product.

trochalcones suggests that in the iodine–amine reactions any configuration control will likewise be of the convergent variety and yield the same isomer ratio from either the *cis*- or *trans*-unsaturated ketone.

Experiments 5 and 6 are notable in the contrast they present to all previous results with the iodine–amine reactions; a significant predominance of the *trans* isomer in the product had always been observed before. Comparison of these experiments with the experiments 1, 2 and 3 performed with *trans*-chalcone demonstrates that the nitro group is responsible for the essentially complete loss of configuration control manifest in ethylenimine ketone formation from the 4-nitrochalcones. This result, which must reflect the electronic influence of the nitro group, may be mediated through a reduction in the basicity of the amino nitrogen atom of an intermediate in which the cyclohexylamino group has taken its place on the β-carbon atom of the unsaturated ketone. One anticipated effect of such a reduction in basicity would be a reduction in the tendency for chelation (as represented in formula V) of a possible intermediate amino enol formed by the conjugate addition of cyclohexylamine to the chalcone. It was suggested previously[5] that the usual predominant formation of *trans*-ethylenimine ketones by the iodine–amine method might be attributed to preferential iodination of such a chelated intermediate from the less hindered side of the chelate ring.[11] If, because of a lesser tendency for chelation, the iodination step frequently occurred at times when the amino enol was not in the chelated conformation, very little steric selectivity should attend the iodination process. As Cromwell[4b,6] has recently pointed out, halogenation of the α-carbon of such an unchelated amino enol might be expected to be sterically non-selective if two groups on the β-carbon, such as phenyl (or *p*-nitrophenyl) and cyclohexylamino, are of nearly the same size.



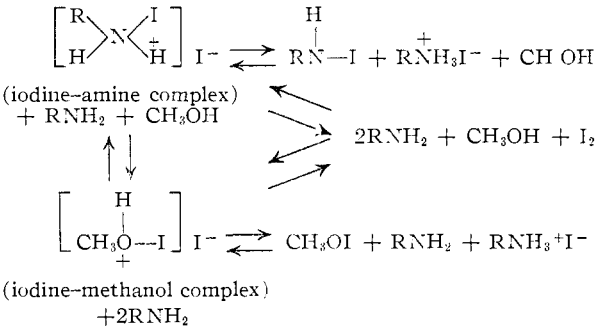
Va, R = Ph
b, R = *p*-$O_2NC_6H_5$ VIa, b VIIa, b

Experiment 4 is a duplicate of experiment 2 except for a shorter reaction time and replacement of the solvent benzene by methanol. Again the mixed ethylenimine ketones were formed in high yield, but the isomer ratio was changed to a very significant degree. The change in the percentage of *trans* isomer from 64 to 88% indicates that the change in the solvent has in some manner altered the reaction process. Since, as discussed below, the use of methanol shifts the isomer ratio in the opposite direction when the same compounds are prepared by the cyclohexylamine–α-bromochalcone reaction, it is most unlikely that these methanol solvent effects merely reflect equilibration of the isomeric ethylenimine ketones after they are formed. It was shown by experiment that cyclohexylamine is insufficiently basic to cause equilibration of the *cis*-ethylenimine ketone Xb when the two compounds were dissolved in benzene solution.

In experiment 7, experiment 5 is duplicated except for substitution of methanol for benzene. Again, as in experiment 4, it is shown that the effect of this solvent change is to increase very markedly the proportion of *trans* isomer in the product. The nitro group is seen to be much less effective in destroying configuration control in methanol than in benzene; in methanol the usual rule that the *trans* isomer will predominate significantly is still observed.

It seems most unlikely that this methanol solvent effect can be attributed to a strengthening, contrary to expectation, of chelation in methanol solution as compared with chelation in benzene solution. However, it is possible that the character of the iodination process is changed in another fundamental manner in changing from benzene to methanol as the reaction solvent. In the relatively polar solvent methanol the exchange of the iodonium ion, I^+, and of protons between the various possible basic carriers should be facilitated, and an additional carrier for both protons and iodonium ions would be present in the form of the alcoholic hydroxyl group.

The following equilibria must be considered possible in such a solution



Thus compounds capable of transferring I^+ to an amino enol might include I_2, $[\overset{+}{R}NH_2I]I^-$, RNHI, $[\overset{+}{C}H_3OHI]I^-$ and CH_3OI. The other iodinating agents would be considerably less bulky than the iodine–cyclohexylamine complex or N-iodocyclohexylamine, and the I^+ ion would in general be less tightly held. Thus the iodination step might be less restricted by steric effects in methanol than in benzene.

It may be suggested that the favored reaction course will be determined by at least three variable steric factors. These include (1) the relative populations among possible conformations of an intermediate amino enol, (2) the sizes and reactivities of the iodinating molecules present in the reaction mixture and (3) the degree of steric hindrance which the various conformations of the amino enol present

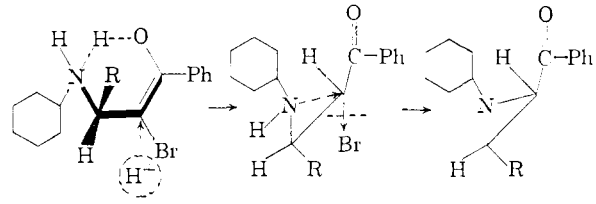
(11) Iodination in such a manner would be expected to yield the *erythro*-α-iodo-β-amino ketones VI, and the indicated internal (neighboring group) displacement would then be expected to invert the configuration at the α-carbon to give the *trans*-ethyleneimine ketones VII. N. H. Cromwell, G. V. Hudson, R. A. Wankel and P. J. Vanderhorst, THIS JOURNAL, **75**, 5384 (1953), have concluded that in similar chloro and bromo amino ketones inversion of configuration at the α-carbon accompanies ring-closure to the ethylenimine ketones.

toward the approach of iodinating agents of different sizes. It might be expected that a highly populated conformation of the amino enol which presented a relatively large hindrance to the approach of an iodinating agent might contribute to the reaction process to a large degree if the iodinating agent were small and highly reactive, but to a slight degree if the iodinating agent were large and less reactive. It has been suggested that β-amino enols may tend to exist preponderantly in a chelated form.[5] However, a chelated amino enol derived from a chalcone and having an N-cyclohexyl group appears likely to be highly hindered to the approach of a large iodinating agent from either side of the chelate ring, although probably approachable by simple I^+ or CH_3OI, etc. The high proportion of *trans*-ethylenimine ketone produced in methanol may indicate that iodination of the chelated amino enol by these agents is occurring readily; the lesser proportion formed in benzene may indicate hindrance to iodination of the *chelated* amino enol by the large iodine–amine complex, and a consequent shift toward iodination of less highly populated open conformations[6] of the amino enol which may present less hindrance.[12]

Recently Cromwell and his associates[4a] have reported an instance in which N-bromocyclohexylamine reacting with an α,β-unsaturated ketone (*p*-phenylcrotonophenone) in benzene solution has yielded chiefly or exclusively the *cis*-ethylenimine ketone. Thus the rule prevailing in the iodine–amine complex reactions that the *trans* isomer should predominate was actually reversed. For reactions conducted in benzene solutions we have confirmed this finding with both *trans*-chalcone and *trans*-4-nitrochalcone (Table I, experiments 8 and 10). The experiment with *trans*-chalcone was not completely satisfactory because the conversion to the ethylenimine ketone was very low (10%), but the product obtained appeared to be essentially pure *cis*-isomer. With *trans*-4-nitrochalcone the degree of configuration control was relatively low, but the *cis* isomer again predominated (57% *cis* isomer). The nearly exclusive formation of the *cis* isomer from *trans*-chalcone is unexpected on the basis of any theory so far advanced.[13] When the same N-bromocyclohexylamine reactions were conducted in methanol the ethylenimine ketone from *trans*-chalcone contained 73% of the *trans* isomer and that from *trans*-4-nitrochalcone 58% of the *trans* isomer. These results are not greatly different from those obtained in methanol with iodine as the halogen; they suggest a very significant difference in mechanism, probably in the bromination step, between the N-bromocyclohexylamine reactions in benzene and those in methanol. Bromination of chelated amino enols by a variety of brominating agents smaller than N-bromocyclohexylamine may have become important in the methanol solution as a result of equilibria such as have been discussed for the iodine–amine–methanol mixture.

In general it appears that *trans*-ethylenimine ketones may be expected to predominate as products of these halogen–primary amine reactions when iodine is the halogen and/or methanol is the solvent. The highest proportion of *trans* isomer can apparently be expected when iodine and methanol are used together.

The pronounced effect on configuration control introduced by changing the solvent for the halogen–amine additions was next observed to have its counterpart in a solvent effect on the configuration of ethylenimine ketones produced by the action of cyclohexylamine on *trans*-α-bromochalcone or *trans*-α-bromo-4-nitrochalcone.[14] Table II records the very pronounced increases in the proportion of *cis* isomer in the ethylenimine ketone product mixtures which we observed when methanol was substituted for benzene in these reactions; the effect of the change of solvent is seen to be the reverse of that encountered in the halogen–amine additions and to be so large as to make the *cis* isomer predominate.[15]

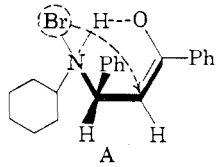


VIIIa, R = Ph
b, R = *p*-$O_2NC_6H_5$ IXa, b Xa, b

It is the *cis* isomer which would be produced if a chelated intermediate α-bromo-β-amino enol (VIII) were protonated preferentially from the side of the chelate ring not shielded by the β-aryl group. Protonation from this direction would produce the *threo*-α-bromo-β-cyclohexylamino ketones (IX) and internal displacement with inversion at the α-carbon[11] would convert IX into the *cis*-ethylenimine ketones (X). In methanol solutions the relatively small molecules of the solvent or protonated solvent would be available to function as the protonating agents. The indicated approach to the α-carbon of the chelated enol is probably not blocked by the cyclohexyl group against protona-

(12) With respect to the possible competition between chelated and open-chain intermediates the situation here may be analogous to that prevailing in additions of organometallic compounds to α-amino or α-hydroxy ketones; see D. J. Cram and K. R. Kopecky, THIS JOURNAL, **81**, 2748 (1959).

(13) A possibility which merits consideration is that N-brominated intermediates such as that pictured in structure A might be formed by N-bromination of the initial amine adduct and might be capable of undergoing bromination at the α-carbon *via* intramolecular transfer of bromine occurring across one side of a chelate ring. The result would be an α-bromo-β-ketone of the *threo*- configuration, leading to a *cis*-



A

ethylenimine ketone. The formation of an analogous intermediate with iodine is less likely

(14) The preparation in ethanol solution of an ethylenimine ketone in what later proved to be the *cis* form was described in one of the early papers on the α-bromo ketone–primary amine reactions; see N. H. Cromwell, R. D. Babson and C. E. Harris, THIS JOURNAL, **65**, 312 (1943).

(15) Less pronounced solvent effects on configuration control have been observed in ketonization of an acyclic enol which cannot undergo chelation; see ref. 6b.

TABLE II

FORMATION OF ETHYLENIMINE KETONES BY THE REACTION OF α-BROMO-α,β-UNSATURATED KETONES WITH CYCLOHEXYLAMINE AT 28°

Expt.	Solvent	Added substance[a]	Other reactant[a]	Reaction time, hrs.: min.	Yield, %	ΔD[b]	% *trans*-ethylenimine
1	Benzene	C	*t*-BrCh	18:00	100	0.140	66
2	Methanol	C	*t*-BrCh	14:40	94	− .078	36
3	Benzene	C	*t*-4NBrCh	2:40	98	.269	84
4	Benzene	C	*t*-4NBrCh	2:40	94	.245	81
5	Methanol	C	*t*-4NBrCh[c]	1:40	92	− .147	20
6	Methanol	*t*-4NBrCh[d]	C	2:30	91	− .129	23

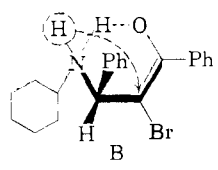
[a] C = cyclohexylamine, *t*-BrCh = *trans*-α-bromochalcone, *t*-4NBrCh = *trans*-α-bromo-4-nitrochalcone; three moles of cyclohexylamine was used for each mole of ketone. [b] Calculated from the infrared spectrum of the mixture; $D_{5.98} - D_{5.90}$ or $D_{5.91}$ (see Experimental section). [c] Initially a slurry, but all solid was dissolved before the addition was completed. [d] Added in portions as the solid; each portion was added after the preceding one had dissolved.

tion by methanol. On the other hand, it is evident that protonation by a bulky cyclohexylammonium ion, as might be required when the reaction occurs in benzene, is likely to be severely hindered. Such hindrance might effectively preclude protonation of the chelated form of an intermediate α-bromo-β-amino enol and divert the reaction toward protonation of some non-chelated conformation[6]; *i.e.*, the preponderant formation of the *cis* isomer in methanol may reflect protonation mainly of the chelated form of the amino enol, the preponderant formation of the *trans* form in benzene may reflect a preferred direction for protonation of open conformations.[16] There would appear to be no simple explanation for the fact that the 4-nitro group confers a greater stereospecificity toward formation of the *cis* isomer in methanol and toward formation of the *trans* isomer in benzene.

In summary, it may be noted that for reactions conducted in methanol the preponderant configuration of the ethylenimine ketone products was correctly predicted both for the chalcone–halogen–cyclohexylamine reactions (mainly *trans* isomer) and for the α-bromochalcone–cyclohexylamine reactions (mainly *cis* isomer) on the basis of hypothetical chelated amino enol intermediates. Predictions based on the same or a similar hypothesis appear also to hold in benzene solution for additions of certain secondary amines to α,β-unsaturated nitro compounds[5] or of morpholine to α-bromochalcones,[1,17,18] for additions of N-bromomorpholine to chalcones,[1,17,18] and for reactions of the iodine–amine reagent with chalcones. However, another explanation, such as that recently advanced by Cromwell and by Zimmerman,[6] clearly must be invoked to account for such results as the predominantly *trans* product formed in benzene in the reaction of cyclohexylamine or methylamine[4a] with α-bromochalcones and for the predominantly *cis* product formed in benzene by reactions of the cyclohexylamine–N-bromocyclohexylamine combination with chalcones.[19] The available data are not extensive, but thus far there is no instance of a reaction in methanol not in accord with the prediction derived from the chelation hypothesis. Further investigation will be required to determine whether configuration control in these conjugate additions is in fact a reflection of the types of possible steric interaction which have thus far been suggested.[20]

Some comment is needed concerning experimental details of the present investigation. The individual isomeric ethylenimine ketones were separated from the reaction mixtures in certain of the experiments in order to corroborate the indication of their presence obtained from the infrared spectra.

(16) Formation of an *erythro*-α-bromo-β-amino ketone leading to a *trans*-ethylenimine ketone could also result from an intramolecular protonation across one side of a chelate ring as pictured in formula B. The availability of such an intramolecular process would be consistent with the observation that the *trans*-ethylenimine ketones were favored



B

in benzene but not in methanol, where protonation from the solvent is possible. This mechanism of protonation has been suggested in the past (N. H. Cromwell, private communication).

(17) P. L. Southwick and W. L. Walsh, THIS JOURNAL, **77**, 905 (1955).

(18) For reactions occurring in benzene solution one possible explanation of the contrast between the tendency to form *erythro* adducts with cyclohexylamine and what are apparently *threo* adducts with morpholine (ref. 1), can be derived from an inspection of models. A β-morpholino group, whether present in a chelated or an unchelated enol, offers much less interference toward protonation at the α-carbon than does a β-cyclohexylamino group. A similar explanation could apply to the contrast between the configurational outcome in reactions of N-bromocyclohexylamine as compared with those of N-bromomorpholine.

An alternative explanation of these differences might be based on the fact that only in reactions involving primary amines would the intramolecular processes depicted in formulas A and B (footnotes 13 and 16) be possible.

(19) In their present form the theories set forth in references 6a and 6b, which emphasize the importance of bulk interactions between groups on the α- and β-carbons and neglect possible intramolecular functional group bonded interactions, do not by themselves appear to provide a complete basis for predicting the steric outcome of the conjugate additions of amines or N-haloamines. In particular, they do not account for the rather high degree of configuration control which can be achieved under favorable conditions even with two groups on the β-carbon as similar in size as phenyl and cyclohexylamino or phenyl and morpholino, nor do they easily explain the effect of solvent changes on the direction of amine and N-haloamine additions. Moreover, they predict the same predominant isomer from the α-bromo ketone–amine reaction as from the ketone–N-bromoamine reaction. This prediction is contrary to fact for a number of reactions conducted in benzene (*cf.* ref. 1 as well as results reported here) and may always be wrong for reactions conducted in methanol.

(20) A systematic study of the various factors which may influence configuration control in the formation of ethylenimine ketones by both of the principal synthetic methods has been undertaken by Prof. N. H. Cromwell and his associates (ref. 4a and private communication). A variety of solvents are being used and starting materials are being chosen to elucidate the effects of changing the halogen from chlorine to iodine, as well as to demonstrate effects of variation in the sizes of substituent groups. Work is in progress in these laboratories on conjugate amine and halogen–amine additions leading to products of other types.

Thus it was shown by a successful isolation experiment that the *cis*-ethylenimine ketone Xa (the minor product) is actually present in the product mixture from the reaction of *trans*-chalcone with cyclohexylamine and iodine.

The calculation of the ratios (percentages) of the isomeric ethylenimine ketones from infrared data depended upon having product mixtures containing no large amounts of other components. (The analytical method would compensate reasonably well for small amounts of most impurities.) Unless otherwise noted, the calculated isomer compositions recorded in the tables were obtained from spectra entirely devoid of bands not associated with one or the other of the pure isomers throughout the measured wave length range (2 to 12 μ in carbon tetrachloride solution). Occasionally enough unchanged unsaturated ketone was present at the end of the reaction period to interfere with the spectroscopic analysis.

An indication of the degree of reproducibility of these experiments is to be found in a comparison of the duplicate experiments 3 and 4 recorded in Table II. It will be observed that the yields agreed within 4% and the percentages of *trans* isomer found within 3%. Experiments 1 and 2 of Table I and 5 and 6 of Table II also represent pairs of duplicate runs except for differences in the reaction period allowed and a change in the order of mixing reactants. Again the results are quite well reproduced. In tests of the analytical method with compounded mixtures of the pure isomers the agreement of the spectroscopically determined isomer composition with the known composition was within 3% or less. The importance of controlling the temperature in these experiments was made evident by comparison of the results of experiments 3 and 4 of Table II and experiments 5 and 6 of Table II with those obtained in parallel experiments in which the temperature was allowed to rise during the reaction. In the experiment in benzene without temperature control the proportion of *trans* isomer fell to 70% as compared to the over 80% observed in experiments 3 and 4. In the uncontrolled experiment in methanol the proportion of *trans* isomer rose to 38%, as compared to about 20% for experiments 5 and 6.

The ethylenimine ketones Xb and VIIb containing the *p*-nitrophenyl group are new compounds. The assignment of the *cis* and *trans* configuration, respectively, to these two compounds was based not only on the position of their infrared carbonyl bands (5.98 μ for VIIb, 5.91 μ for Xb)[8] but also on the results of their reactions with phenylhydrazine. Cromwell[8] has shown that ethylenimine ketones of the *cis* configuration react with phenylhydrazine to give pyrazoles, whereas the *trans* isomers give aminopyrazolines. Compound Xb yielded 1,3-diphenyl-5-(*p*-nitrophenyl)-pyrazole when treated with phenylhydrazine; compound VIIb yielded 1,3-diphenyl-4-cyclohexylamino-3-(*p*-nitrophenyl)-Δ^2-pyrazoline. Thus the configurational assignments for these isomers seem firmly established.

Acknowledgment.—The authors are much indebted to Professor Norman H. Cromwell for discussion contributing to the interpretation of results set forth in this paper.

Experimental[21]

Reactions of Chalcones with Iodine and Cyclohexylamine (Table I). **General Procedure.**—The reactions were performed with anhydrous solvents in a three-neck flask fitted with a thermometer, a stirrer and a dropping funnel. The flask was partly immersed in a thermostated water-bath, and the temperature of the reaction mixture was maintained at 28 ± 0.5°. A solution containing one of the reactants was slowly added through the funnel to a stirred solution of the other reactants in the flask. When the reaction was completed, the mixtures were worked up as described below.

Benzene reaction mixtures were diluted with ether and filtered to remove cyclohexylamine hydroiodide. The filtrates were washed with ten 100-ml. portions of water, dried over magnesium sulfate, and evaporated to dryness without heating. The crude products were analyzed by the method described below.

Methanol reaction mixtures were poured into 300–500 ml. of water, and the mixtures were extracted with three portions of ether. The ether extracts were washed with ten 100-ml. portions of water, dried over magnesium sulfate and evaporated without heating. Occasionally, it was necessary to add magnesium sulfate to the mixtures during the washing process in order to break up emulsions which tended to form. The crude mixtures were analyzed as described below.

Individual Experiments.—Listed below for the numbered experiments in Table I are (A), the volume of solvent containing the added reactant; (B), the volume of solvent containing the material in the flask; (C), the number of moles of the starting ketone; and (D), the time required for mixing the solutions: expt. 1: (A) 5 ml., (B) 20 ml., (C) 0.007 mole, (D) 40 min.; expt. 2: (A) 15 ml., (B) 10 ml., (C) 0.007 mole, (D) 40 min.; expt. 3: (A) 15 ml., (B) 10 ml., (C) 0.002 mole, (D) 50 min.; expt. 4: (A) 15 ml., (B) 10 ml., (C) 0.007 mole, (D) 40 min.; expt. 5: (A) 35 ml., (B) 25 ml., (C) 0.008 mole, (D) 1 hr.; expt. 6: (A) 35 ml., (B) 25 ml., (C) 0.005 mole, (D) 1 hr., 40 min.; expt. 7: (A) 45 ml., (B) 60 ml., (C) 0.020 mole, (D) 1 hr.

Reactions of Chalcones with Cyclohexylamine and N-Bromocyclohexylamine (Table I). **General Procedure.**—A solution of the ketone and four molar equivalents of cyclohexylamine in the solvent of choice was allowed to stand overnight at room temperature. A solution of one molar equivalent of bromine was slowly added to this solution. The methods of mixing the solutions and working up the reaction mixtures were identical to those described above for the iodine–cyclohexylamine reactions.

Individual Experiments.—Listed below for the numbered experiments in Table I are (A), the volume of solvent containing the bromine; (B), the volume of solvent containing the ketone and cyclohexylamine; (C), the number of moles of ketone employed; and (D), the time required for mixing the solutions: expt. 8: (A) 10 ml., (B) 10 ml., (C) 0.007 mole, (D) 1 hr., 15 min.; expt. 9: (A) 10 ml., (B) 10 ml., (C) 0.007 mole, (D) 35 min.; expt. 10: (A) 10 ml., (B) 30 ml., (C) 0.006 mole, (D) 30 min.; expt. 11: (A) 10 ml., (B) 30 ml., (C) 0.006 mole, (D) 40 min.

Reactions of α-Bromochalcones with Cyclohexylamine (Table II). **General Procedure.**—In all the reactions but one, a solution of cyclohexylamine in the solvent of choice was added to a stirred solution of the α-bromo-α,β-unsaturated ketone. In the remaining reaction (expt. 6), solid *trans*-α-bromo-4-nitrochalcone was added to a stirred solution of cyclohexylamine in methanol. The mixing of the reactants, the work-up of the mixtures and the analysis of the crude products conformed to the general description outlined for the iodine–cyclohexylamine reactions.

Individual Experiments—Listed below for the numbered experiments in Table II are (A), the volume of solvent containing the added substance; (B), the volume of solvent containing the substance in the reaction flask; (C), the number of moles of the α-bromochalcone employed; and (D), the time required for mixing reactants: expt. 1: (A) 5 ml., (B) 15 ml., (C) 0.007 mole, (D) 8 min.; expt. 2: (A) 5 ml., (B) 15 ml., (C) 0.007 mole, (D) 10 min.; expt. 3: (A) 5 ml., (B) 35 ml., (C) 0.006 mole, (D) 40 min.; expt. 4: (A) 5 ml., (B) 35 ml., (C) 0.006 mole, (D) 40 min.; expt. 5: (A) 5 ml., (B) 35 ml., (C) 0.006 ml., (D) 40 min.; expt. 6: (B) 20 ml., (C) 0.003 mole, (D) 20 min.

(21) Melting points are corrected. Microanalyses are by Drs. G. Weiler and F. B. Strauss, Oxford, England.

Infrared Analysis of Product Mixtures.—Quantitative determinations of isomer percentages were based upon comparison of the intensities of carbonyl bands observed for the reaction product mixtures with those of the pure *cis*- and *trans*-ethylenimine ketones. In the case of the *trans* isomers the carbonyl bands for both the 2-phenyl compound and the 2-*p*-nitrophenyl compound were at 5.98 μ, whereas in the case of the *cis* isomers the band for the 2-phenyl compound was at 5.91 μ, that for the 2-*p*-nitrophenyl compound at 5.90 μ. Using mixtures compounded from purified samples of the individual *cis*- and *trans*-2-phenyl compounds, separate plots were obtained for the 5.98 and 5.91 μ bands of optical density, D, *vs.* the percentage of *trans* isomer present. Similar plots for the 5.98 and 5.90 μ bands were made for mixtures of the two isomeric 2-*p*-nitrophenyl compounds. The absorptions used in constructing these plots are recorded in Table III. All measurements were made with a Perkin–Elmer model 21 Spectrophotometer on solutions containing 30 mg./ml. of the compound or mixture in carbon tetrachloride.

Optical densities for the carbonyl bands were calculated from observed values of percentage transmittance which had been adjusted slightly in accordance with slight variations in the transmittances of certain selected reference bands which were found to be common to both isomers and of almost exactly the same intensity in both. The transmittances of these reference bands, obtained by averaging measurements on pure isomers and mixtures compounded from pure isomers, were: (1) for the 2-phenyl compounds, $T_{3.43\,\mu} = 35.9\%$, $T_{6.25\,\mu} = 72.1\%$, $T_{6.69\,\mu} = 81.1\%$, $T_{6.90\,\mu} = 43.2\,\mu$; (2) for the 2-*p*-nitrophenyl compounds, $T_{3.42\,\mu} = 42.8\%$, $T_{6.24\,\mu} = 50.4\%$, $T_{6.56\,\mu} = 21.7\%$, $T_{6.90\,\mu} = 49.8\%$. Corrections to be applied to carbonyl transmittances of reaction product mixtures were obtained by averaging deviations at the four reference bands from the expected transmittances.

TABLE III

1-Cyclohexyl-2-phenyl-3-benzoylethylenimines			1-Cyclohexyl-2-(*p*-nitrophenyl)-3-benzoylethylenimines		
trans-Isomer, %	$D_{5.91}$	$D_{5.98}$	*trans*-Isomer, %	$D_{5.90}$	$D_{5.98}$
0	0.524	0.176	0	0.441	0.140
20.3	.433	.241	24.2	.333	.220
37.3	.358	.286	49.7	.233	.286
63.0	.243	.370	71.6	.172	.352
81.1	.162	.415	100	.045	.428
100	.067	.469			

In the plots obtained from measurements on the compounded mixtures of pure isomers (Table III) all points fell close to the best straight line drawn by visual inspection through the plotted values. (The maximum deviation was equivalent to an error of *ca.* 3% in the percentage of *trans* isomer found.) There was no apparent deviation from the Lambert–Beer law. Except where noted in Table I, the spectra of the reaction product mixtures, after preparation as described above, showed no bands in the range 2–12 μ other than those associated with one of the two isomeric ethylenimine ketones. When unchanged starting material was present this was evident from the infrared spectrum.

The determination of percentages of isomers in reaction product mixtures involved the use of the line plots of optical densities *vs.* percentage *trans* isomer for both carbonyl bands. The plots for both bands were combined into a single chart from which percentage compositions could be read from the difference of optical densities (equivalent to the difference of the $-\log_{10}$ of the transmittances) at the carbonyl wave lengths for the two isomers. This was equivalent, in the case of the 2-phenyl compounds, to the use of the following equation, based upon Lambert–Beer law equations and the assumption that the mixtures consisted wholly of the isomeric ethylenimine ketones

$$\%\ trans = \frac{D_{5.98} - D_{5.91} - (E_{5.98}{}^{cis} - E_{5.91}{}^{cis})}{E_{5.98}{}^{trans} - E_{5.91}{}^{trans} - (E_{5.98}{}^{cis} - E_{5.91}{}^{cis})} \times 100$$

The constants $E_{5.98}{}^{cis} = 0.184$, $E_{5.91}{}^{cis} = 0.532$, $E_{5.98}{}^{trans} = 0.466$ and $E_{5.91}{}^{trans} = 0.080$ are the optical densities expected for solutions (30 mg./ml. in carbon tetrachloride) of the two pure isomers at the indicated wave lengths, the numerical values having been obtained from the intercepts of the linear plots described above. For the 2-*p*-nitrophenyl compounds the constants used in the corresponding equation would be $E_{5.98}{}^{cis} = 0.156$, $E_{5.90}{}^{cis} = 0.434$, $E_{5.98}{}^{trans} = 0.427$, $E_{5.90}{}^{trans} = 0.052$.

With other methods of treating the infrared data, calculated percentages for reaction products mixtures were occasionally at variance with the proportion of isomers made evident by the over-all appearance of the spectrum of the mixture.

As measured in carbon tetrachloride solution in the range 2.0–12 μ, the infrared bands of the four different ethylenimine ketones involved in this study occurred at the wave lengths listed below. (The more prominent bands are indicated by the letter s.)

trans-1-Cyclohexyl-2-(*p*-nitrophenyl)-3-benzoylethylenimine (VIIb): 3.42s, 3.51, 5.98s, 6.24s, 6.32, 6.56s, 6.70, 6.90s, 7.19, 7.31, 7.45s, 7.63, 7.75, 8.08s, 8.21s, 8.34, 8.49, 9.03, 9.58, 9.87, 9.96s, 10.31, 11.14, 11.62, 11.85 μ.

cis-1-Cyclohexyl-2-(*p*-nitrophenyl)-3-benzoylethylenimine (Xb): 3.42s, 3.51, 5.90s, 6.24s, 6.31, 6.56s, 6.69, 6.90s, 7.14, 7.34s, 7.44s, 7.62, 8.04, 8.20s, 8.50, 8.70, 9.62, 9.76, 9.85, 10.06, 11.06, 11.45, 11.72s μ.

trans-1-Cyclohexyl-2-phenyl-3-benzoylethylenimine (VIIa)[8a]: 3.31, 3.43s, 3.51, 5.98s, 6.25, 6.32, 6.69, 6.90s, 7.13s, 7.23, 7.44, 7.65, 8.07s, 8.20s, 8.35, 8.50, 9.58, 9.71, 9.95s, 11.14 μ.

cis-1-Cyclohexyl-2-phenyl-3-benzoylethylenimine (Xa)[8a]: 3.31, 3.43s, 3.51, 5.91s, 5.99, 6.25, 6.32, 6.69, 6.90s, 7.08, 7.32s, 7.44, 7.54, 7.65, 8.05, 8.20s, 8.51, 8.70, 9.12, 9.38, 9.60, 9.86, 10.08, 11.00, 11.60 μ.

Preparation of *trans*- and *cis*-1-Cyclohexyl-2-(*p*-nitrophenyl)-3-benzoylethylenimines.—To a stirred slurry of 5.0 g. (0.0198 mole) of *trans*-4-nitrochalcone and 7.8 g. (0.079 mole) of cyclohexylamine in 100 ml. of benzene was added a solution of 5.0 g. (0.0198 mole) of iodine in benzene over a 20-minute period. No heating occurred during the addition. The mixture was stirred for another 4.5 hours and then worked up according to the general procedure described above for iodine–cyclohexylamine additions. The products consisted of 8.6 g. (96%) of cyclohexylamine hydroiodide and 6.8 g. (97.5%) of crude ethylenimine, m.p. 80–100°.

Crystallization from 50 ml. of ethanol gave 1.7 g. of crude *cis*-ethylenimine, m.p. 92–115°. Concentration of the mother liquor afforded 2.5 g. of crude *trans*-ethylenimine, m.p. 92–97°. Repeated crystallization of the *cis* isomer afforded an analytical sample as short light yellow needles, m.p. 127–128° dec. Further crystallization of the *trans* isomer from petroleum ether (b.p. 30–60°) afforded an analytical sample as a light-yellow powder, m.p. 107–109° dec. A mixed melting point of the two isomers was 95–101° dec.

Anal. Calcd. for $C_{21}H_{22}O_3N_2$: C, 71.98; H, 6.33; N, 8.00. Found (*trans* isomer): C, 71.63; H, 6.18; N, 7.95. (*cis* isomer): C, 71.57; H, 6.43; N, 8.25.

The ultraviolet spectrum of the *trans* isomer in 95% ethanol (Cary recording spectrophotometer) showed maxima at 257 mμ (ϵ 18,600) and 276–279 mμ (ϵ 16,300). Minima were at 229 mμ (ϵ 6,480) and 275 mμ (ϵ 16,200). The spectrum of the *cis* isomer showed maxima at 251 mμ (ϵ 16,700) and 279–283 mμ (ϵ 12,100). Minima were at 227 mμ (ϵ 5,790) and 270 mμ (ϵ 11,700).

Reactions of *trans*- and *cis*-1-Cyclohexyl-2-(*p*-nitrophenyl)-3-benzoylethylenimines with Phenylhydrazine. *trans* **Isomer.**—A solution of 1.2 g. (0.0036 mole) of the *trans* isomer, 0.39 g. (0.0036 mole) of phenylhydrazine and 0.43 g. (0.0072 mole) of acetic acid in a mixture of 12 ml. of chloroform and 8 ml. of absolute ethanol stood at room temperature for 14 hours and then in a refrigerator for 10 hours. The solution was diluted with ether and washed with water. Drying and evaporation gave an orange oil. Crystallization from petroleum ether (b.p. 65–110°) afforded 0.36 g. of small, orange prisms, m.p. 170–175°. Further crystallization from petroleum ether afforded an analytical sample; 0.14 g., small, orange prisms, m.p. 180–181.5°. The compound gave a positive Knorr pyrazoline test[22]; a deep blue color was generated when a dilute ferric chloride solution was added to a dilute solution of the compound in 9:1 sulfuric acid–water.

Anal. Calcd. for $C_{27}H_{28}N_4O_2$: C, 73.61; H, 6.41; N, 12.72. Found: C, 73.67; H, 6.25; N, 12.90.

The ultraviolet spectrum in 95% ethanol showed maxima at 248 mμ (ϵ 22,800), 287.5–290 mμ (ϵ 14,200) and 352 mμ (ϵ 21,600). Minima were at 220 mμ (ϵ 16,400), 274 mμ (ϵ

(22) L. Knorr, *Ann.*, **238**, 200 (1887).

13,500) and 315 mμ (ε 11,300). The chemical, analytical and spectroscopic evidence indicated that the product was 1,3-diphenyl-4-cyclohexylamino-5-(*p*-nitrophenyl)-Δ^2-pyrazoline.

cis **Isomer.**—A solution of 2.1 g. (0.0063 mole) of the *cis* isomer, 0.68 g. (0.0063 mole) of phenylhydrazine and 0.75 g. (0.0126 mole) of acetic acid in a mixture of 18 ml. of chloroform and 12 ml. of absolute ethanol stood at room temperature for 14 hours and then in a refrigerator for 10 hours. The darkened solution was diluted with ether, washed with water, dried, and evaporated. The resulting orange oil was crystallized from petroleum ether (b.p. 65–110°), giving 0.66 g. of orange needles, m.p. 133–139°. Two crystallizations from petroleum ether gave an analytical sample; 0.24 g., small, yellow prisms, m.p. 139–140°. The compound gave a negative Knorr test for a pyrazoline.

Anal. Calcd. for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31. Found: C, 73.86; H, 4.20; N, 12.4.

The ultraviolet spectrum in 95% ethanol showed maxima at 242.5 mμ (ε 22,100) and 265 mμ (ε 25,000). Minima were at 227.5 mμ (ε 20.500) and 245 mμ (ε 22,000). The chemical, analytical and spectroscopic data indicated that the product was 1,3-diphenyl-5-(*p*-nitrophenyl)-pyrazole.

Test of Configurational Stability of *cis*-1-Cyclohexyl-2-(*p*-nitrophenyl)-3-benzoylethylenimine (Xb).—A solution of 0.25 g. (0.0007 mole) of the *cis*-ethylenimine ketone and 0.07 g. (0.0007 mole) of cyclohexylamine in 5 ml. of benzene was allowed to stand at 28° for 60 hours. The mixture was diluted with ether, washed with water and dried over magnesium sulfate. Evaporation of the solvents yielded 0.21 g. of white powder, m.p. 119–123° dec. The infrared spectrum of the material indicated that it represented the original *cis* compound in nearly pure form.

Isolation of *cis*-1-Cyclohexyl-2-phenyl-3-benzoylethylenimine from the Reaction of Cyclohexylamine and Iodine with *trans*-Chalcone.—A solution of 3.54 g. (0.014 mole) of iodine in 30 ml. of benzene was added to a stirred solution of 2.90 g. (0.014 mole) of chalcone and 5.52 g. (0.056 mole) of cyclohexylamine in 20 ml. of benzene over a period of 30 minutes. The temperature remained at 28°. After the mixture was stirred for another 110 minutes, filtration gave 6.10 g. (97%) of cyclohexylamine hydroiodide. The filtrate was worked up as were other cyclohexylamine–iodine additions to give 3.98 g. (96%) of crude product.

A 1.5-g. portion of the product was dissolved in 50 ml. of petroleum ether (b.p. 65–110°). After refrigeration, 0.56 g. of a solid, m.p. 89–95°, was filtered out. The filtrate was concentrated to 20 ml. and allowed to stand overnight at room temperature to afford 0.14 g. of a solid, m.p. 90–98°. This material was dissolved in 5 ml. of petroleum ether (b.p. 30–60°) and refrigerated to give 0.05 g. of needles, m.p. 100–104°. A mixed melting point with *trans*-1-cyclohexyl-2-phenyl-3-benzoylethylenimine was 80–87°. A mixed melting point with *cis*-1-cyclohexyl-2-phenyl-3-benzoylethylenimine was 100–106°. The infrared spectrum of the material was determined in a carbon tetrachloride solution (30 mg./ml.) and showed a band for band correspondence with a similarly determined spectrum of *cis*-1-cyclohexyl-2-phenyl-3-benzoylethylenimine,[8a] m.p. 106–107°.

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[CONTRIBUTION FROM ORGANIC RESEARCH DEPARTMENT, RESEARCH DIVISION, ABBOTT LABORATORIES]

Specific Solvent Effects in the Alkylation of Enolate Anions. I. The Alkylation of Sodiomalonic Esters with Alkyl Halides

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The pseudo-first-order rate constants for the alkylation of sodio-1-methylbutylmalonic ester with ethyl bromide and of sodio-*n*-butylmalonic ester with *n*-butyl bromide and iodide have been measured in benzene solution at several temperatures and in the presence of varying concentrations of many polar additives. Certain N,N-disubstituted amides and several coordinate covalent N-, P- and S-oxides distinguish themselves from many other polar substances by increasing alkylation rates many-fold at less than 5% concentrations. Evidence is presented to show that this striking rate acceleration is most likely produced by a specific solvation of sodium ion which tends to dissociate the high molecular weight ion-pair aggregate of the sodio-derivative that exists in benzene solution.

The scope of current activity in the study of tautomeric substances and of ambient anions derivable from them witnesses to the importance of this field to both theoretical and practical organic chemistry. Brady and Jakobovits[1] have investigated the effect of varying the cation on the reactivity of many ambient anions. Brändström[2] has been concerned with the effect of the degree of dissociation of the metal derivatives on their reactivities and reaction paths. Kornblum and his co-workers[3a] have undertaken an extensive investigation of the reactions of silver and alkali metal nitrites with alkyl halides, and have formulated a general principle relating the reaction path to the character of the transition state. Zook and Rellahan[4] have examined the alkylation of sodium enolates of alkyl phenyl ketones from a similar point of view; Hauser and co-workers[5] have long been interested in the acylation of enolate anions; and Curtin[6] and Kornblum[3b] and their students have analyzed, from differing points of view, the effect of a number of factors controlling the position of alkylation of alkali metal salts of phenols.

Even the stereochemistry of these substances has been scrutinized. Zimmerman[7] has studied the stereochemical mode of protonation of enolate anions, and Kabachnik and his associates[8] have demonstrated the presence of both *cis*- and *trans*-enolic forms in many α-substituted acetoacetic esters.

Although many kinetic studies of the alkylation of β-ketoesters have been reported,[2a] the only such investigation with malonic esters seems to be that of Pearson.[9] He determined the second-

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