[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, UNIVERSITY COLLEGE, LONDON]

Ethylenimine Ketones. XIV.[1] Steric Controls in Conjugate Additions

BY NORMAN H. CROMWELL[2]

RECEIVED DECEMBER 8, 1958

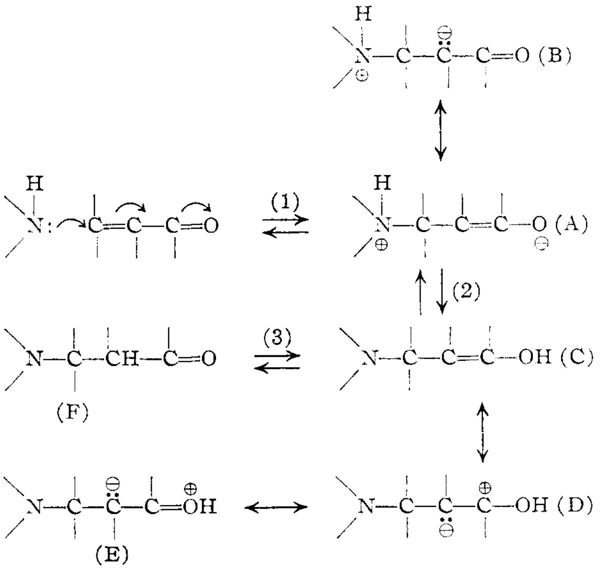
A new correlation is given between steric controls and the data which have been gathered during the synthesis of the *cis* and *trans* aryl aroyl ethylenimines and alkyl aroyl ethylenimines by reaction of α-bromo-α,β-unsaturated ketones with amines, and from the reaction of an α,β-unsaturated ketone with bromine-amine mixtures under various conditions. Steric controls during a ketonization step in these reactions are based on the relative effective size of the groups attached to both the asymmetric β-tetrahedral carbon and the α-trigonal carbon of the enol tautomer of the intermediate α-halo-β-aminoketones. These effects are related to the factors of asymmetric induction experienced with reactions of acyclic systems wherein a new asymmetric center is created adjacent to an old one by means of 1,2-additions at carbonyl and oxime groups.[3]

Asymmetric induction during the synthesis of molecules which already contain an asymmetric carbon atom has been recognized for many years. Perhaps the most extensive correlation of the stereochemical direction of asymmetric induction in acyclic systems and the arrangement of groups according to their effective bulk at the asymmetric carbon already present in the molecule is that reported by Cram.[3] A rule was formulated which was successful in correlating and predicting the stereochemical direction of asymmetric induction in reactions of acyclic systems in which a new asymmetric center is created adjacent to an old one by means of 1,2-additions to carbonyl groups or the reduction of oximino groups to amines. Cram[3] pointed out that it is often difficult to arrange the groups in such systems according to their effective bulk.

In a previous publication[4] it was stated that an attempt to extend this rule of steric control of asymmetric induction[3] to explain the stereochemistry operating during the reactions of amines with α-bromo-α,β-unsaturated ketones did not lead to the proper predictions. This led us to what we have since decided[1] was probably an unsound conclusion, namely, that the ketonization step in these reactions does not involve an sp^2 α-carbon of the enol structure.[5]

It has never been definitely established that amines add in a 1,4-fashion, rather than in a 1,2-manner to α,β-unsaturated ketones (C^1—C^2—C^3—O^4). Nevertheless, some of the details of the 1,4-mechanism were discussed by the author several years ago.[6] It seems quite probable that the first step (1) in a 1,4-addition reaction would involve bonding of the unshared electrons of the nitrogen of the amine to the electron deficient β-carbon atom of the α,β-unsaturated ketone.

Although a significant contribution would not be expected from D and E to the resonating system C $\longleftrightarrow$ D $\longleftrightarrow$ E, it is somewhat less certain that a contribution by B to the system A $\longleftrightarrow$ B is to be dismissed without consideration of the possible ability of the positive charge on the nitrogen to attract the electrons from the π-bond of the carbonyl enol anion A toward the electron distribution suggested by B. Nevertheless, the basic assumption is now made that the oxygen in these systems does develop the negative charge as in A and rapidly captures a proton in step 2 to form the enol C in the normal manner.[7] The enol C then ketonizes (*e.g.*, is protonated) in step 3 to form the α-halo-β-aminoketone F in the reactions under consideration.



The main concern of the present communication is to correlate the experimental data which has been obtained in the several studies of these reactions with the relative effective size of the groups attached to both the asymmetric β-tetrahedral carbon and the α-trigonal carbon of the enol intermediates C of the α-halo-β-aminoketones. In the previous paper[4] it was pointed out that the composition of the *erythro–threo* mixture of the α-bromo-β-aminoketones is known from the analysis of the ring-closed product mixture, the *cis*- and *trans*-ethylenimine ketones.

As Cram[3] has warned, it may be difficult to make *a priori* judgments as to the relative *effective* size

---

(1) For paper XIII in this series see, N. H. Cromwell and Roger P. Cahoy, THIS JOURNAL, **80**, 5524 (1958).

(2) Department of Chemistry, University of Nebraska, Lincoln, Neb.

(3) See D. J. Cram and F. A. A. Elhafez, THIS JOURNAL, **74**, 5828 (1952), and references cited therein.

(4) N. H. Cromwell, *et al.*, *ibid.*, **79**, 922 (1957).

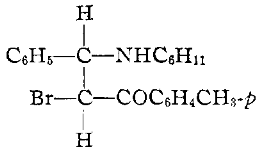
(5) In an interesting series of papers, H. E. Zimmerman, *J. Org. Chem.*, **20**, 549 (1955), and subsequent articles, has shown that under non-equilibrating conditions the less stable ketone isomer is formed by the addition of Grignard reagents to various α,β-unsaturated ketones, the implication being that the transition state of the protonation step involves the α-carbon in the sp^2 state of the enol rather than in the sp^3 state of the carbanion.

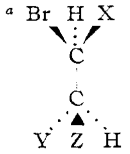
(6) N. H. Cromwell, *Chem. Revs.*, **38**, 83 (1946).

(7) See (a) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 565–568 and 694; (b) G. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1941, pp. 467–470.

TABLE I

SUMMARY OF EXPERIMENTAL EVIDENCE

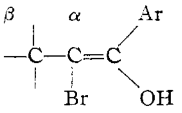
	Major α-bromo-β-aminoketone intermediate[a]			Ethylenimine ketone[b]		
In T. S. 1	X	Y	Z	% *trans*	% *cis*	Ref.
M, CH_3NH L, C_6H_5	$COC_6H_4C_6H_5$-*p*	CH_3NH	C_6H_5	68	31	See Exptl.
M, CH_3 L, NHC_6H_{11}	$COC_6H_4C_6H_5$-*p*	CH_3	NHC_6H_{11}	34	62	4
M, CH_3NH L, C_6H_5	$COC_6H_4CH_3$-*p*	CH_3NH	C_6H_5	60	..	9 See Exptl.
M, NH_2 L, $C_6H_4NO_2$-*p*	COC_6H_5	H_2N	$C_6H_4NO_2$-*p*	78	..	10
(M ~ L) L or M, C_6H_5 M or L, NHC_6H_{11}	 H, C_6H_5—C—NHC_6H_{11}, Br—C—$COC_6H_4CH_3$-*p*, H *erythro* ≅ *threo*			40	45	9



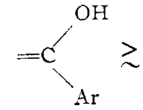
[a] (structure above)

[b] All tabulated results were obtained from reactions carried out in benzene solution. Somewhat different results may be expected if the reaction is done in a protonating solvent (*i.e.*, alcohols) which may compete with the conjugate acid of the amine in the protonation step.

of complex groups in such complex systems as these. It has recently been found, for example, that bromine may be large relative to phenyl in certain substituted ethanes.[8] However, it might seem reasonable enough (though not definite) that one could assign the following relative effective sizes to the groups in the enols with which we are concerned in these reactions. These assignments might be made after a qualitative consideration of the classical relative repulsive forces which are assumed to be mainly of the van der Waals type.



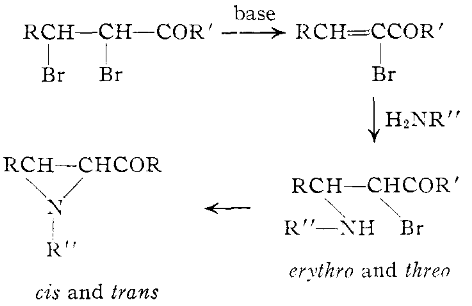
On the asymmetric β-carbon atom
Aromatic > CH_3NH > NH_2 > H
$C_6H_{11}NH$ ~ C_6H_5 > CH_3 > H
On the trigonal α-carbon atom



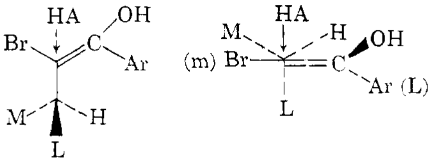
$\gtrsim$ Br >> H

It is possible that in *these systems*, =C(OH)Ar is slightly larger than Br although Br may be slightly larger than phenyl in some systems.[8]

If the basic assumption is made that ketonization (proton transfer) in these reactions takes place *via* a transition state in which the geometry of the enol is not much distorted, then the rest of the conclusions relative to effective bulk of groups and favored conformations in the transition states follows from an examination of the experimental results and models. Following this procedure one may draw representations of the most favored transition states for these reactions as indicated below. The over-all reactions involved are



The experimental results in Table I and a qualitative examination of scale models suggest that the most favored conformation of the enol with the least crowding of groups is as indicated in the drawings, T. S. 1, for the transition state with the protonating agent approaching the enolic double bond in the least hindered manner, namely, from the side of the conformation occupied by the two smaller groups on the β-asymmetric carbon atom. The *cis* arrangement in the enol of the aromatic group (Ar) with respect to the asymmetrically substituted β-carbon has been casually chosen since the solvated hydroxyl (or in this case $-\overset{\ominus}{O}-\overset{\oplus}{N}H_2R_2$) group may be more space demanding. In the last experiment of Table I, where two of the groups on the asymmetric carbon are of comparable size, the amounts of the two products are nearly equal as might be expected.



side view *T. S. 1* *end view*

The reaction[11] of 8-bromoperinaphthenone-7 (I) with cyclohexylamine to produce only the

---

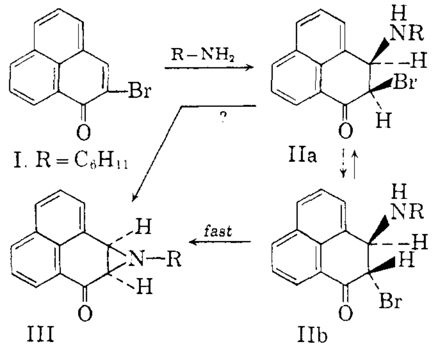
[8] See P. M. Nair and J. D. Roberts, THIS JOURNAL, **79**, 4565 (1957), who report on the residence times of the rotational conformations of $BrCF_2-CBr_2C_6H_5$, using nuclear magnetic resonance spectra.

[9] N. H. Cromwell, *et al.*, *ibid.*, **73**, 1044 (1951).

[10] N. H. Cromwell and G. D. Mercer, *ibid.*, **79**, 3819 (1957).

[11] N. H. Cromwell, D. B. Capps and S. E. Palmer, *ibid.*, **73**, 1226 (1951).

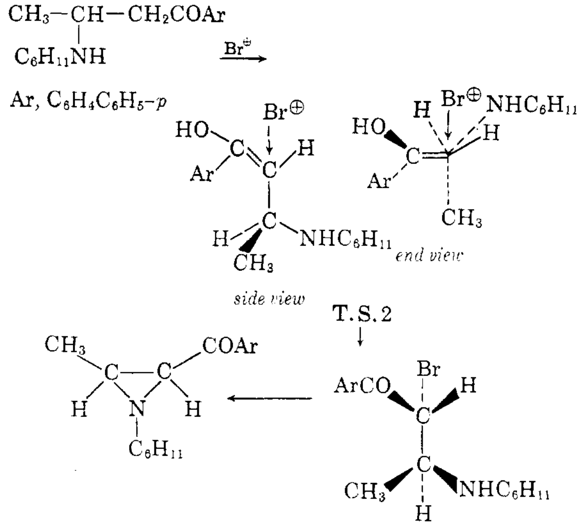
ethylenimine ketone III, and none of the isomeric 8-cyclohexylamino or 9-cyclohexylamino-7-peri-naphthenones, could hardly have been predicted. Ketonization through protonation of the enol intermediate might have been expected[5] to produce the less stable α-bromo-β-aminoketone, IIa, having a configuration in which the bromine atom and the amino groups are *cis* to each other. Ring closure by the normal internal SN2 type reaction to produce the ethylenimine ketone is not possible with this configuration. Either ring closure proceeds by some other mechanism in this case, or the more stable configuration IIb of the intermediate α-bromo-β-cyclohexylamino ketone becomes available in the reaction mixture, possibly through equilibration between IIa and IIb, or from a direct transfer of a proton from the protonated nitrogen to the α-carbon of (A)$\leftrightarrow$(B) in this rigid system.



The details of the reactions of α,β-unsaturated ketones with halogens and amines are even less well understood than are the reactions between amines and α-bromo-α,β-unsaturated ketones. In general an α,β-unsaturated ketone reacts with a mixture of iodine and a primary amine to produce only the *trans* aryl or alkyl aroylethylenimine[4,12,13] and the stereochemical course of these reactions appears to be insensitive to the relative size of the groups on the asymmetric carbon atoms.[4]

Southwick[13c] has suggested that ketonization (iodination) takes place with a chelated enolic intermediate thus producing mainly the *erythro*-α-iodo-β-aminoketone which then ring-closes to give the *trans*-ethylenimine ketone as the major product. It is possible that if α-iodo-β-aminoketones are actually formed in these reactions they may be more subject to racemization than are the α-bromo-β-aminoketones.[4] It is well known that α-iodo ketones ionize to produce the iodine cation and the ketone anion more readily than α-bromo ketones ionize to produce bromine cations and the ketone anion. Such a racemization could lead to the equilibration of the α-iodo-β-amino ketone to favor the *erythro* form which would be expected to close the three-ring to form the *trans*-ethylenimine ketone more rapidly than the ring closure of the *threo* form to produce the *cis*-ethylenimine ketone.

Only one α,β-unsaturated ketone has been studied using bromine and cyclohexylamine under various conditions.[4] Thus *cis*-1-cyclohexyl-2-methyl-3-(*p*-phenylbenzoyl)-ethylenimine was the only product isolated in good yields from, (a) treating a benzene solution of *p*-phenylcrotonophenone and four molar equivalents of cyclohexylamine with one molar equivalent of bromine, (b) the reaction of a benzene solution of one molar equivalent each of the unsaturated ketone and cyclohexylamine with one molar equivalent of the preformed N-bromocyclohexylamine, and (c) the reaction of a benzene solution of one molar equivalent of β-cyclohexylamino-*p*-phenylbutyrophenone with one equivalent of N-bromocyclohexylamine. It is quite probable that all of these reaction series involve a ketonization (bromination) to produce the α-bromo-β-aminoketone intermediate. A chelated intermediate[13c] does not seem to be involved in this reaction. If the mechanism of bromination is as suggested above then the production of the *cis* product in this case can be correlated with the relative size of the groups in the enol intermediate and the rule of asymmetric induction.[3]


$CH_3-\underset{C_6H_{11}NH}{CH}-CH_2COAr \xrightarrow{Br^{\oplus}}$

In transition state, T. S. 2, the least crowded conformation is one in which the double bond of this enol is flanked by the two smaller groups, CH_3 and H, and the brominating agent approaches the double bond from the least hindered side. *p*-Phenylcrotonophenone reacts with a mixture of iodine and cyclohexylamine to produce mainly, if not exclusively, the *trans*-1-cyclohexyl-2-methyl-3-*p*-phenylbenzoylethylenimine ketone rather than the *cis* isomer.[12] It is obvious that the course of these halogen amine reactions of α,β-unsaturated ketones depends to some extent upon the nature of the halogen used.

It is hoped that the further experiments being carried out with these reactions which include the use of iodine, bromine and chlorine and various primary amines, as well as variations in the unsaturated ketone structures will extend our understanding of the steric controls operating in these reactions.

Acknowledgment.—This work was supported by the John Simon Guggenheim Memorial Foundation

---

[12] N. H. Cromwell and R. J. Mohrbacher, THIS JOURNAL, **75**, 6252 (1953).

[13] (a) P. L. Southwick and R. D. Christman, *ibid.*, **74**, 1886 (1952); (b) **75**, 629 (1953); (c) P. L. Southwick and J. E. Anderson, *ibid.*, **79**, 6222 (1957).

to whom the author is grateful for a fellowship award.

Experimental

Reaction of α-Bromo-4′-phenylchalcone with Methylamine.—A 5.1-g. (0.014 mole) sample of α-bromo-4′-phenylchalcone[4] in 50 ml. of benzene was mixed with a cold ether solution containing about 0.05 mole of methylamine. After standing at room temperature for 10 hours and at 5° for 12 hours the methylamine hydrobromide was removed by filtration and the ether–benzene filtrate concentrated to produce 4.1 g. (92% yield) of a pale-yellow colored mixture of the *cis* and *trans* forms of 1-methyl-2-phenyl-3-(*p*-phenylbenzoyl)-ethylenimine, m.p. 102–114°. An 0.8-g. sample of this mixed product was dissolved in benzene and placed on a 20 × 2 cm. column packed with 50 g. of activated alumina. The column was developed with 200 ml. of 1:100 abs. ethanol–dry benzene solution. The eluent was 2:100 abs. ethanol–dry benzene. The initial eluates contained the low-melting *trans* isomer (0.52 g., 68% of total material recovered, m.p. 120–121°). The final eluates contained the higher-melting, *cis* isomer (0.24 g., 31% of total recovered, m.p. 140°). The isolation of 0.76 g. of material represents a 95% recovery. These products were colorless in contrast with the lightly colored materials previously obtained from the corresponding dibromoketone.[14]

Reaction of α-Bromo-4′-methylchalcone with Methylamine.—A 4.25-g. (0.014 mole) sample of α-bromo-4′-methylchalcone was dissolved in 40 ml. of benzene and mixed with an ether solution containing about 0.05 mole of methylamine. After standing at room temperature for 24 hours the usual working up of the reaction mixture gave an oily product, 3.25 g., which was apparently a mixture of the *cis* and *trans* forms of 1-methyl-2-phenyl-3-(*p*-toluyl)-ethylenimine. Chromatographic separation on activated alumina gave in the first eluates the *trans* isomer (1.88 g., 60% of recovered material, m.p. 76–78°).[9] The final eluates, which probably contained mainly the *cis* isomer, produced 1.26 g. (40% of recovered material) which was an oil that was not crystallized. The total material recovered was 3.14 g.

---

(14) N. H. Cromwell and M. A. Graff, *J. Org. Chem.*, **17**, 414 (1952).

LINCOLN, NEBRASKA

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, RUTGERS, THE STATE UNIVERSITY]

The Metalation of 1,7-Dimethoxynaphthalene[1]

BY RODERICK A. BARNES AND WALTER M. BUSH[2]

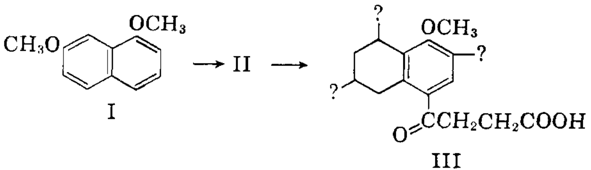
RECEIVED JANUARY 8, 1959

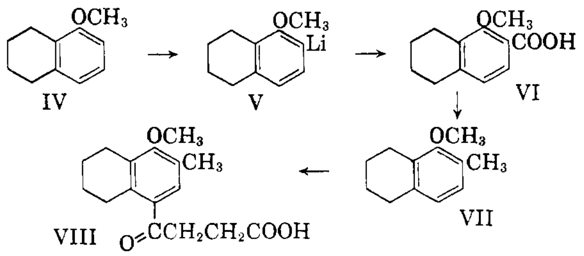
It has been demonstrated that 1,7-dimethoxynaphthalene is metalated in good yield at the 6-position. The bearing of this observation on the mechanism of the metalation reaction has been discussed.

The substitution reactions of 1,7-dimethoxynaphthalene (I) were of interest in connection with synthetic experiments directed toward 19-nor-steroids[3]; the metalation of I was examined because it seemed likely that this reaction would introduce a substituent into a different position from the usual electrophilic aromatic substitutions.

When compound I was metalated by butyllithium in ether and the resulting lithium derivative treated with dimethyl sulfate, a crystalline methyl-1,7-dimethoxynaphthalene (II) could be isolated; the reaction of the lithium derivative with carbon dioxide and N-methylformanilide also produced crystalline substances. In all of the three experiments the yields were about 70% and there was no evidence for the presence of more than one isomer in the products. From this it was concluded that the lithium atom had entered almost exclusively at a single position of compound I.

The structure proof for II was carried out using a two-stage reduction to remove the β-methoxy group; the resulting liquid tetralin derivative was characterized by converting it to the β-aroylpropionic acid (III) with the methyl group almost certainly in one of the three positions *ortho* to the methoxyl groups of I. One of the possible structures for III was synthesized from 5-methoxytetralin (IV). The metalation of IV has not been observed previously, but the structures of the products in this reaction sequence are correct because cleavage of the ether function of VI produced the previously known 5-hydroxy-1,2,3,4-tetrahydro-6-naphthalenecarboxylic acid.[4] The direct transformation of the aryllithium V to the methyl derivative VII was attempted, but the conversion of IV to V proceeds so poorly that the problem of separating pure VII from a much larger amount of unreacted IV was impractically difficult. However, acid VI was readily separated from the starting material and after reduction, first with lithium aluminum hydride and then with palladium and hydrogen, yielded pure VII. The aroylpropionic acid VIII from this series of reactions melted at 119–121.5°, while III melted at 158–160.5°; therefore compound I was not metalated at the 2-position.





The second possibility was synthesized starting from β-(2-bromo-5-methoxyphenyl)-ethyl tosylate

---

(1) Presented before the Division of Organic Chemistry, 128th Meeting of the A. C. S., Minneapolis, Minn., September 15, 1955.

(2) The major portion of this communication is abstracted from a thesis presented to the Graduate Faculty for the Ph.D. degree, May, 1955.

(3) R. A. Barnes and W. M. Bush, THIS JOURNAL, **80**, 4714 (1958).

(4) W. Hückel and E. Goth, *Ber.*, **57**, 1290 (1924).