The stabilities of **1**, **4**, and **2b** were checked under the conditions of the kinetic runs. It was found that **1** and **4** are stable, whereas the aminoindenone **2b** showed a slight decomposition, at 45° after 12 hr. The dilution (100 times or more) at room temperature, quenched the studied reactions.

Two different techniques were used depending on the temperature. For the kinetics run at 30° or below, a sealed bulb containing the amine was crushed in the solution of **1** (or **4**); then the level was rapidly adjusted. Collecting of the samples was done by direct pipeting, and the reaction was quenched by dilution. At least eight measurements were made in each run. The kinetics run above 30° were carried out using the sealed-bulb method. The bulbs were filled with a special weight buret at low temperature to avoid the loss of amine.

In the case of the kinetics followed by uv spectroscopy, the concentrations of the reactant (**1** or **4**) and the product (**2b**) were deduced from the optical densities at four wavelengths. It was noted that only the optical densities of the maxima give significant results. From an average of these values the concentrations of reactant and product were calculated.

For each experiment the following expressions were plotted against time: $\log [a/(a - x)]$, $[1/(b - a)] \log [a(b - x)/b(a - x)]$ (second-order and 1 equiv of amine per 1 equiv of halogeno ketone); $[1/(b - 2a)] \log [a(b - 2x)/b(a - x)]$ (second-order and 2 equiv of amine per 1 equiv of halogeno ketone); a and b are the initial concentrations of the ketone and the amine respectively; x is the concentration of the product. The kinetic constants were determined by the least-squares method; the precision is estimated at about ±3%.

The titration of the bromide ions was carried out as follows. A sample (5 or 10 ml) of the reaction medium was poured into 80 ml of benzene. The bromide ions were carefully extracted three times with 15 ml of distilled water, and the organic solvents were removed under vacuum at room temperature. The bromide ions were titrated by Volhard's method. This procedure permits a selective titration of the bromide ions, without interference with any other component.

The amine-consumption was followed by titrating the remaining amine. The sample was poured in a separating funnel containing 10 ml of 4×10^{-2} *N* HCl solution covered by 70 ml of benzene. After shaking, the aqueous layer was collected and the benzene layer was extracted three times by 15 ml of distilled water. The organic solvents were removed from the water solution under vacuum and the remaining acid was titrated (using methyl red as indicator) by an 8×10^{-3} *N* solution of morpholine in methanol. This procedure prevented the formation of the hydrochloride of the aminoindenone **2b** and permitted the selective titration of the diisopropylamine.

Registry No.—**1**, 5387-50-8; **2a**, 5387-51-9; **2a** HBr, 15982-75-9; **2b**, 15982-76-0; **2c**, 15984-15-3; **2d**, 15982-77-1; **2e**, 15982-78-2; **2f**, 15982-79-3; **2g**, 15982-80-6; **3a**, 5387-52-0; **3a** HCl, 15982-82-8; **3c**, 15982-83-9; **3d**, 15982-84-0; **3e** HCl, 15982-85-1; **3f**, 15982-86-2; **3g**, 15982-87-3; **3h**, 16031-03-1; **3j**, 15982-88-4; **3k**, 15983-89-8; **4**, 15983-91-2; 3-methoxy-2-benzal-1-indanone, 15984-14-2.

Acknowledgments.—The senior author (N. H. C.) is grateful for the hospitality afforded him by the Department of Chemistry during his tenure in 1967 as a guest of the Massachusetts Institute of Technology and for helpful discussions with Professor H. O. House during the later phases of this investigation. We also wish to thank Professor G. A. Gallup for his suggestions in the programming of the MO calculations. The work was supported in part by Grant No. CA02931 from the National Cancer Institute of the U. S. Public Health Service.

Mobile Keto Allyl Systems. VII.[1a] Amine-Exchange Reactions in the Indanone–Indenone Series

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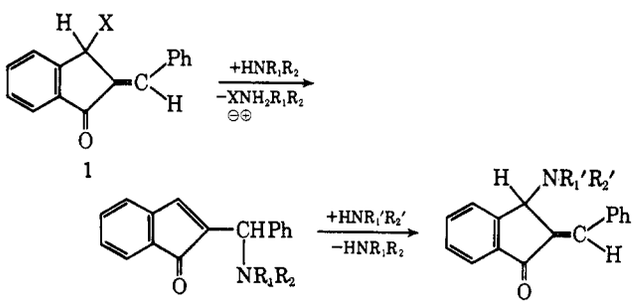
2-[α-(Substituted amino)benzyl]-1-indenones are shown to undergo a second-order amine-exchange reaction with certain amines to produce 3-substituted amino-2-benzal-1-indanones. For example, 2-[α-(diisopropylamino)-benzyl]-1-indenone undergoes this aminotropic allylic rearrangement with the less space-demanding amines (morpholine, piperidine, pyrrolidine, and *t*-butylamine) but not with diisopropylamine. The course of the reactions was followed by employing nmr, tlc, kinetic, and ultraviolet absorption techniques. It is proposed that these aminotropic allylic changes are best explained by a variant of an SN2′ mechanism. A novel amine-catalyzed prototropic rearrangement of the 3-(substituted amino)-2-benzal-1-indanones to 3-(substituted amino)-2-benzyl-1-indenones was also established.

In the preceding paper of this series,[1a] it has been shown that the reaction of 3-halogeno-2-benzal-1-indanones (**1**) with primary and secondary amines proceeds in two steps to give first the 2-(α-aminobenzyl)-1-indenones (**2**) then the isomeric 3-amino-2-benzal-1-indanones (**3**).

On the basis of various kinetic studies, a nearly concerted bimolecular mechanism was assigned to the first allylic rearrangement **1** → **2**. In the present paper, the results of our studies of the second allylic rearrangement **2** → **3** are reported.

The displacement of allylic amino groups with amines is expected to be relatively difficult, and reports of the use of an amine as the displacing reactant are very rare in the literature. Some allylamines resulting from the



2a, $R_1 = R_2 = i$-Pr
b, R_1 = H; $R_2 = t$-Bu
c, R_1 = H; $R_2 = i$-Pr

3a, R_1, R_2 = morpholino
b, R_1, R_2 = piperidino
c, R_1, R_2 = pyrrolidino
d, R_1 = H; $R_2 = t$-Bu
e, R_1 = H; $R_2 = i$-Pr

(1) (a) For paper VI in this series, see G. Maury, E.-M. Wu, and N. H. Cromwell, *J. Org. Chem.*, **33**, 1900 (1968); (b) Abstracted in part from the Ph.D. thesis of E.-M. Wu, University of Nebraska, Lincoln, Neb., 1966; (c) the author to whom all correspondence concerning this article should be addressed.

normal or abnormal substitution of an halogeno allyl system by amines have been shown to be stable, while the corresponding allyl halide often undergoes a rearrangement under the same conditions. N,N-Diethyl-α-methylallylamine and N,N-diethyl-γ-methylallylamine or their salts appear to be stable under relatively severe conditions.[2,3] Recently, it was reported that the dimethylamino group in 17aα-dimethylamino-17aβ-methyl-D-homoandrosten-17-one is displaced by primary or secondary amines entering in position 16 (the carbonyl being enolized).[4] Finally, another example of an allylic amino group displaced by an amine was found in the series of 2[α-(N-*t*-butylamino)benzyl]-acrylophenone which reacts with *t*-butylamine or piperidine to give rearranged α-(aminomethyl)chalcones.[5,6]

Results

A. Amine-Exchange Reactions.—The aminoindenones **2** were prepared as previously described[1] by condensation of 3-bromo-2-benzal-1-indanone with the corresponding amines. However, not all aminoindenones **2** are suitable for the study of this rearrangement. Because of their relative stability and their ability to be purified, only the solid aminoindenones **2** were investigated. This included the aminoindenones derived from bulky amines, isopropylamine, *t*-butylamine, and diisopropylamine.

2-[α-(Diisopropylamino)benzyl]-1-indenone (**2a**) did not react with diisopropylamine at room temperature. For this reason, this compound was chosen to study the replacement of the amino group in **2** by a series of amines. The reaction of **2a** with morpholine occurred very easily at room temperature in benzene or acetonitrile and gave 3-morpholino-2-benzal-1-indanone (**3a**) and diisopropylamine; the allylic system was reversed and the amino group exchanged. This reaction was also followed by nmr at −5°, and the only detected products were diisopropylamine and **3a**; no intermediate was found by thin layer chromatography (tlc).

The reaction of **2a** with piperidine proceeded faster under the same conditions and gave the corresponding indanone **3b** in quantitative yield. The reaction was quite similar in the case of pyrrolidine which gave the indanone **3c** also in high yield. With *t*-butylamine no change was observed in benzene, while in acetonitrile the reaction went to completion only after 5 days at 22° (compared with times of 5 hr, 10 min, and 5 min with morpholine, piperidine, and pyrrolidine, respectively) and gave 3-(*t*-butylamino)-2-benzal-1-indanone (**3d**) as the only product. Such differences in reaction rates appear to be related to the steric demand of the entering amine rather than to its basicity. It is to be noted that the reaction of **2a** with *t*-butylamine takes place at room temperature, while the reaction of 2-[α-(*t*-butylamino)benzyl]-1-indenone (**2b**) with diisopropylamine does not take place under the same conditions, although the basicity of diisopropylamine is higher than that of *t*-butylamine. The rates of the preceding reactions are influenced by the nature of the solvent and are slower in benzene than in acetonitrile.

The resulting aminoindanones **3** have been characterized mainly by nmr and uv and, more precisely, by the large uv absorption between 300 and 320 mμ due to the 2-benzal-1-indanone structure.[1]

The same exchange reaction, in a case in which the released amine is susceptible to reaction with the starting aminoindenone, was also studied.

$$\mathbf{2b} + t\text{-Bu-NH}_2 \longrightarrow \mathbf{3d} + t\text{-Bu-NH}_2$$

$$\mathbf{2c} + i\text{-Pr-NH}_2 \longrightarrow \mathbf{3e} + i\text{-Pr-NH}_2$$

The reaction of **2b** with *t*-butylamine in acetonitrile at room temperature was followed by tlc and the products analyzed by nmr; only **3d** and *t*-butylamine were detected. Similarly, the reaction of 2-[α-(isopropylamino)benzyl]-1-indenone (**2c**) with isopropylamine in chloroform gave only 3-(isopropylamino)-2-benzal-1-indanone (**3c**) and isopropylamine, as seen by nmr and tlc.

The general case of the preceding amine-exchange reactions occurs when the amino groups in each of the two reactants are different and when the released amine (different from the starting amine) can react further with the aminoindenone.

$$\mathbf{2c} + t\text{-Bu-NH}_2 \xrightarrow{k_1} \mathbf{3d} + i\text{-Pr-NH}_2 \qquad (1)$$

$$\mathbf{2c} + i\text{-Pr-NH}_2 \xrightarrow{k_2} \mathbf{3e} + i\text{-Pr-NH}_2 \qquad (2)$$

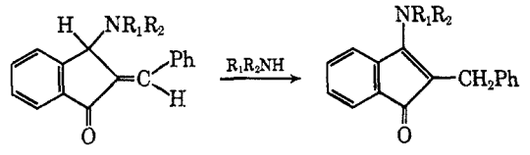
The reaction of **2c** with *t*-butylamine in deuteriochloroform at 22° was followed by nmr. The aminoindanone **3d**, formed with a relatively low rate, was first detected; then the signals of the indanone **3e** appeared and their intensity increased faster than the signals of **3d**. These results are explained by the occurrence of two simultaneous, interdependent reactions 1 and 2: formation of **3d** and isopropylamine and subsequent attack of the indenone **2c** by isopropylamine with a rate greater than that with *t*-butylamine. This difference in rates explains also the apparent production of only the aminoindanone **3e** in the reaction of **2b** with isopropylamine in deuteriochloroform at 25°; the indanone **3d**, probably formed to a very little extent, could not be detected by nmr.

The 2-benzal-1-indanone structure is known to be more stable than the isomeric 2-benzyl-1-indenone structure, and therefore the aminoindanones **3** are expected to react with amines with more difficulty than the aminoindenones **2**. Nevertheless, an amine-exchange reaction was found when 3-piperidino-2-benzal-1-indanone (**3b**) was allowed to react with a large excess of morpholine in benzene, and 3-morpholino-2-benzal-1-indanone (**3a**) resulted in good yield. The reaction was followed by tlc, and no intermediate was detected. However, this does not exclude the possibility of two successive allylic rearrangements giving first 2-(α-morpholinobenzyl)-1-indenone (this compound has been prepared in another reaction[1]) as intermediate, and then 3-morpholino-2-benzal-1-indanone formed by immediate reaction of the amine in excess with the aminoindenone. Also, the present results do not rule out the occurrence of the direct SN2 substitution.

B. Prototropic Rearrangement of Keto Allylamines.—The base-catalyzed prototropic rearrangement of

(2) W. G. Young, I. D. Webb, and H. L. Goering, *J. Amer. Chem. Soc.*, **73**, 1076 (1951).
(3) W. G. Young, R. A. Clement, and C. Shih, *ibid.*, **77**, 3061 (1955).
(4) D. F. Morrow, M. E. Butler, W. A. Neuklis, and R. M. Hofer, *J. Org. Chem.*, **32**, 86 (1967).
(5) R. P. Rebman and N. H. Cromwell, *Tetrahedron Lett.*, 4833 (1965).
(6) N. H. Cromwell and R. P. Rebman, *J. Org. Chem.*, **32**, 3830 (1967).

allyl systems has been extensively studied.[7] However, reports of isomerization of allylic amines, with an amine as catalyst, seem to be nonexistent in the literature.



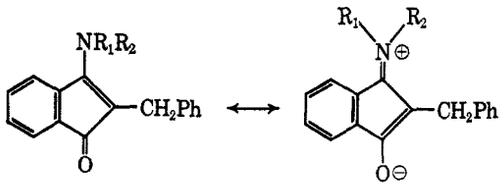
3

4a, R_1 = H; R_2 = *t*-Bu
b, R_1, R_2 = piperidino
c, R_1, R_2 = morpholino

It was found that on treatment with an excess of amine in benzene the aminoindanones **3** undergo a prototropic shift giving the corresponding 3-amino-2-benzyl-1-indenones (**4**). 3-*t*-(Butylamino)-2-benzal-1-indanone (**3d**) reacted with an excess of *t*-butylamine in benzene at room temperature to give a 60% yield of 3-(*t*-butylamino)-2-benzyl-1-indenone (**4a**) as the only product. On refluxing in benzene the same reaction occurred with an increased rate.[8] In acetonitrile at 100°, in the presence of a large excess of diisopropylamine, 2-[α-(*t*-butylamino)benzyl]-1-indenone (**2b**) gave the indenone **4a** as the main product, probably by an amine-catalyzed prototropic isomerization of the intermediate **3d**, formed by decomposition of the starting indenone and subsequent reaction of **2b** with the released amine.

The base-catalyzed rearrangement of 3-piperidino-2-benzal-1-indanone (**3b**) with piperidine in excess was also investigated. Under the same conditions (refluxing benzene), the reaction afforded 3-piperidino-2-benzyl-1-indenone (**4b**); the yield of the rearranged product was increased by increasing the concentration of amine and the reaction time. The analogous 3-morpholino-2-benzyl-1-indenone (**4c**) was also obtained from the interaction of 3-morpholino-2-benzal-1-indanone (**3a**) with an excess of morpholine in refluxing xylene; the yield was increased from 15 to 42% by increasing the concentration of amine.

The assignment of the 3-amino-2-benzyl-1-indenone structure to compounds **4** was established by spectral data and by acid hydrolysis to the known 2-benzyl-1,3-indandione.[10] As Vanags and coworkers have pointed out,[11] the uv spectra of the 3-amino-1-indenones have four maxima at about 220, 250–280, 370, and 430 mμ. All of these absorptions are observed in the uv spectra of the indenones (**4**). In particular, the band between 250 and 280 mμ (a doublet) is to be compared with the high-intensity doublet found at 237–243 mμ in the uv spectra of the 2-(α-aminobenzyl)-1-indenones (**2**).[1] This doublet probably corresponds to an electron-transfer transition comparable to that observed for acetophenone.[12] The preceding bathochromic shift is expected if the β-enamino ketone resononace contributes to the excited state.[13]



Kinetic Results

The kinetic study reported here deals with the allylic rearrangement of 2-(α-aminobenzyl)-1-indenones on reaction with an amine. As in the kinetic study of the first step of the reaction of the bromo ketone **1** with amines, we have used the large differences in uv absorptions of reactant **2** and product **3** to follow kinetically the reaction.

As suggested by the preceding results,[1] the reactions of 2-[α-(diisopropylamino)benzyl]-1-indenone with morpholine and with piperidine, in acetonitrile, were found to be second order, first order in both aminoindenone and amine. The energy of activation of the reaction involving morpholine is relatively small, and the rate of the reaction increases when piperidine is used; this effect is normal since piperidine is expected to be a stronger nucleophile than morpholine under these conditions. (See Tables I and II.)

TABLE I

VALUES OF THE SECOND-ORDER RATE COEFFICIENTS k_2 FOR THE REACTION OF 2-[α-(DIISOPROPYLAMINO)BENZYL]-1-INDENONE WITH MORPHOLINE, IN ACETONITRILE

t, °C	[Aminoindenone], mole/l.	[Morpholine], mol/l.	$10k_2$,[a] l. mol^{-1} min^{-1}
18.3	0.00987	0.0390	1.6
18.3	0.0200	0.0633	1.4
18.7	0.00593	0.0992	1.6
29.9	0.0203	0.0419	2.6
30.0	0.00624	0.0232	2.7
30.0	0.00664	0.0281	2.6
44.1	0.00589	0.0185	4.5

[a] $k_2 = Ae^{E/RT}$; E = 8.0 kcal/mol; $A = 1.5 \times 10^5$ l. mol^{-1} min^{-1}.

TABLE II

VALUES OF THE SECOND-ORDER RATE COEFFICIENTS k_2 FOR THE REACTION OF 2-[α-(DIISOPROPYLAMINO)BENZYL]-1-INDENONE WITH PIPERIDINE, IN ACETONITRILE

t, °C	[Aminoindenone], mol/l.	[Piperidine], mol/l.	k_2, l. mol^{-1} min^{-1}
30.0	0.00628	0.00461	5.0
30.0	0.00634	0.00557	5.4[a]
30.0	0.00639	0.00700	4.7[a]
30.0	0.00876	0.00876	5.0

[a] Coefficients calculated using the method of S. Widequist: K. B. Wilberg, "Physical Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1964, p 318.

The reaction of 2-[α-(*t*-butylamino)benzyl]-1-indenone with *t*-butylamine in acetonitrile was found to be pseudo first order in aminoindenone. This result was expected since, in the exchange of amine, the concentration [B] of *t*-butylamine remains constant and equal

(7) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965, p 193.

(8) It has been previously reported that 2-[α-(*t*-butylamino)benzyl]-1-indenone is also formed in this reaction,[9] but this has not been confirmed in our further studies reported here.

(9) N. H. Cromwell and E.-M. Wu, *Tetrahedron Lett.*, 1499 (1966).

(10) G. Vanags and T. Dumpis, *Dokl. Akad. Nauk SSSR*, **125**, 549 (1959).

(11) Y. Freimanis and G. Vanags, *J. Gen. Chem. USSR*, **30**, 3328 (1960); **34**, 448 (1964).

(12) (a) A. I. Scott, "Interpretation of the Ultra Violet Spectra of Natural Products," Pergamon Press Inc., New York, N. Y., 1964, p 100.

(13) R. D. Campbell and N. H. Cromwell, *J. Amer. Chem. Soc.*, **79**, 3456 (1957).

TABLE III

VALUES FOR THE SECOND-ORDER RATE COEFFICIENTS k_2 IN THE REACTION OF 2-[α-(*t*-BUTYLAMINO)BENZYL]-1-INDENONE WITH *t*-BUTYLAMINE, IN ACETONITRILE

t, °C	[Aminoindenone], mol/l.	[*t*-Butylamine], mol/l.	10^2k_2,[a] l. mol^{-1} min^{-1}
16.9	0.0182	0.0574	1.2
16.9	0.0282	0.0785	1.2
16.9	0.0424	0.0466	1.3
25.9	0.0289	0.0737	1.9
25.9	0.0395	0.0513	2.1
25.9	0.0483	0.0629	1.9
34.9	0.0224	0.0730	2.7
34.9	0.0309	0.0482	2.6
34.9	0.0390	0.0624	2.6

[a] $k_2 = Ae^{E/RT}$; E = 8 kcal/mol.

to the initial concentration $[B_0]$; the differential equation becomes the following. (See Table III.)

$$\frac{d[A]}{dt} = k[A][B] = k'[A] \quad \text{with } k = \frac{k'}{[B_0]}$$

Similarly, the reaction of 2-[α-(isopropylamino)benzyl]-1-indenone with isopropylamine in chloroform was pseudo first order in aminoindenone (see Table IV).

TABLE IV

VALUES FOR THE SECOND-ORDER RATE COEFFICIENTS k_2 IN THE REACTION OF 2-[α-(ISOPROPYLAMINO)BENZYL]-1-INDENONE WITH ISOPROPYLAMINE, IN CHLOROFORM

t, °C	[Aminoindenone], mol/l.	[Isopropylamine], mol/l.	10^2k_2,[a] l. mol^{-1} min^{-1}
17.8	0.0237	0.0622	6.7
17.8	0.0281	0.1250	6.7
17.9	0.0314	0.0780	7.5
17.9	0.0326	0.0706	7.6
22.9	0.0189	0.0624	8.8
22.9	0.0225	0.0331	8.3
22.9	0.0279	0.0471	8.5
27.9	0.0166	0.0493	14.7
27.9	0.0200	0.0414	15.2
27.9	0.0251	0.0606	14.1

[a] $k_2 = Ae^{E/RT}$; E = 13 kcal/mol.

In the general case of the amine exchange (see, for example, eq 1 and 2), the rate coefficient k_2 can be measured if the kinetics corresponding to eq 2 are followed separately. Moreover, the corresponding system of differential equations gives a relation 3 between x and y (x and y being the concentrations of the indenone having reacted in reactions 1 and 2, respectively); a and b are the initial concentrations of the

$$\left.\begin{aligned} \frac{dx}{dt} &= k_1(a - x - y)(b - x) \\ \frac{dy}{dt} &= k_2(a - x - y)x \end{aligned}\right\} \left(\frac{k_1}{k_2}\right)y = b \ln \frac{b}{b - x} - x \quad (3)$$

indenone and the amine, respectively. At the end of the reaction, the sum $x + y$ is equal to a; if the ratio x/y is also known (by integration of the corresponding signals in the nmr spectrum), it is possible to calculate x and y and then the ratio k_1/k_2. This ratio permits a direct comparison of the reactivities of the two amines toward the starting aminoindenone in the same conditions. However, this method is valid only if the precision of the measurements is good; in the reaction of **2c** with *t*-butylamine in deuteriochloroform, we found a ratio k_1/k_2 of about 0.05 at 22°.

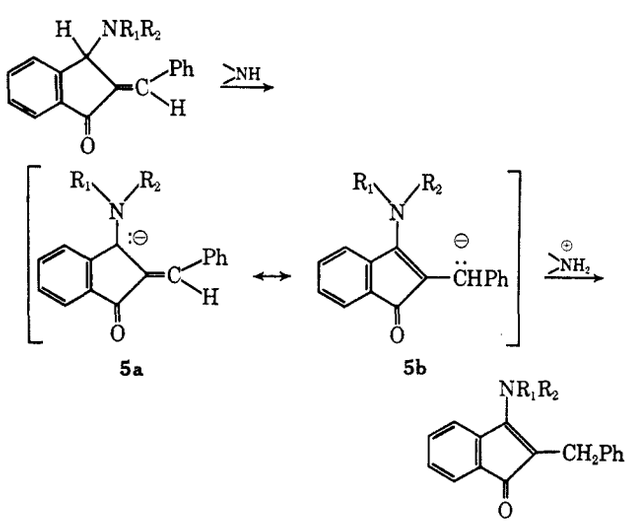
Discussion

As in the reaction of 3-halogeno-2-benzal-1-indanone with amines,[1] two extreme mechanisms can be proposed for the reaction of 2-(α-aminobenzyl)-1-indenone with amines: a concerted SN2′ mechanism, or a nonconcerted amine exchange involving a 1,4 addition of the amine $HNR_1'R_2'$ to the α-enone system, followed by loss of the amine HNR_1R_2 in a second step (Scheme I).

A nonconcerted amine exchange would imply the formation of an intermediary diamino ketone adduct which was never detected in any of the studied reactions. The influence of the size of the amine (*e.g.*, *t*-butylamine, morpholine, and piperidine, reacting with **2a**) shows the existence of steric effects between the entering and the leaving amino groups. This suggests that the amino groups are *cis* to each other in the transition state of a concerted, or nearly concerted, process. The SN2′ nature of the reaction is then favored since the "*cis*" structure of the SN2′ transition state has been demonstrated.[14] A *cis* relationship would be expected to be favored by establishment of hydrogen bonding between the two nitrogens in the transition state; this might be proved by a kinetic study similar to the study of Dittmer and Marcantonio in the case of α-methylallylchloride[15] where no hydrogen participation was observed.

By analogy with the first step of the reaction **1** → **2**, the preceding results support for the second step **2** → **3** a variant of an SN2′ mechanism.[1] This mechanism differs with that of a "pure" SN2′ process because in our case the developing negative charge in the transition state is probably partially supported by the oxygen of the carbonyl (*cf.* the resonance of the α-enone system) as well as by the departing amino group. This distribution of the charges is unsymmetrical as opposed to the symmetrical distribution in the transition state of a "pure" SN2′ reaction.

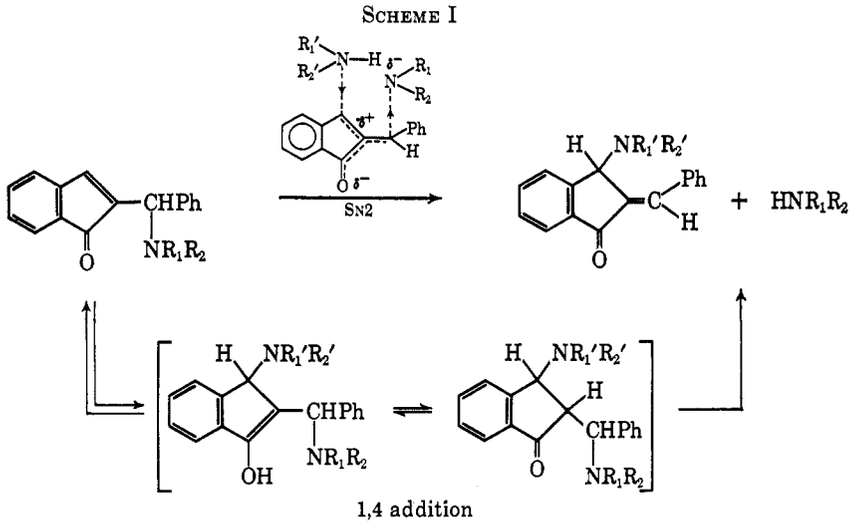
The prototropic rearrangement of 3-amino-2-benzal-1-indanones (**3**) to 3-amino-2-benzyl-1-indenones (**4**) in the presence of an excess of amine probably involves the carbanion **5** in which the proton adjacent to the nitrogen has been abstracted by a molecule of amine. The allylic carbanion **5** is normally stabilized by resonance and



(14) G. Stork and W. N. White, *J. Amer. Chem. Soc.*, **78**, 4609 (1956).

(15) D. C. Dittmer and A. F. Marcantonio, *Chem. Ind.* (London), 1237 (1960).

SCHEME I



the localization of the negative charge on the exocyclic benzylic carbon **5b** is more likely than on the carbon adjacent to the nitrogen **5a**. It is also possible that the carbanion **5** is further stabilized by homoconjugation with the carbonyl.[16]

Experimental Section[17]

I. Amine-Exchange Reactions.—3-Bromo-2-benzal-1-indenone (**1**) and the aminoindenones **2a** and **2b** were prepared as previously described.[1]

Preparation of 2-[α-(Isopropylamino)benzyl]-1-indenone (2c).—To a solution of 0.50 g of **1** in 15 ml of benzene–*n*-hexane (50:50), 2 equiv of isopropylamine (0.20 g) was added at 0–5°. The hydrobromide of the amine precipitated and was filtered: 0.15 g (65%). The solvent was partially evaporated at room temperature, and the residue taken up in benzene and immediately chromatographed on a column of neutral alumina. By rapid elution with benzene, two fractions were obtained: (1) 0.145 g of a bright yellow viscous oil which was shown to be pure by tlc [ether–petroleum ether (bp 30–60°), 50:50]; (2) 0.01 g of a yellow oil containing the preceding compound (higher R_f) and another pale yellow product. The first fraction solidified giving a bright yellow solid which was recrystallized in *n*-hexane at room temperature (precipitation at −60°), mp 68–69°. Ultraviolet maxima, mμ (ε), in *n*-hexane were found at 237 (41,000), 243 (43,000), 308 (1300), 371 (1350), 330 (1050), and 387 (820); in chloroform, 246 (42,800), 321 (1600), and 392 (700). Nmr peaks were detected between τ 2.3 and 3.2 (9 H aromatic and 1 H vinylic), at 5.17 (1 H benzylic, doublet, J = 1.3 cps), 7.22 (1 H isopropyl, quintet by superimposition of two quartets, J = 6.5 cps), 8.33 (NH), 8.92 (methyl isopropyl, doublet, J = 6.5 cps), 8.98 (methyl isopropyl doublet, J = 6.5 cps).[18]

Anal. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.91; N, 5.05. Found: C, 82.08; H, 7.00; N, 5.13.

Preparation of 3-(Isopropylamino)-2-benzal-1-indanone (3e).—The preceding reaction was repeated with 0.30 g of **1** and 0.12 g of isopropylamine in 10 ml of benzene at room temperature. The reaction was followed by tlc (ether–petroleum ether, 50:50). Two main spots were observed: a bright yellow spot belonging to **2c** and a pale yellow spot which was shown to belong to **3e**. After 5-hr reaction time, the first tlc spot had completely vanished. After 8 hr, 0.12 g (85%) of isopropylamine hydrobromide were filtered. The evaporation of the solvent left 0.18 g of a pale yellow solid, mp 104–105° (*n*-hexane). Ultraviolet maxima, mμ (ε), in *n*-hexane were found at 228 (13,400), 234 (12,600), 252 (sh) (9300), 304 (sh) (22,100), 312 (23,000), 327 (sh) (15,200); in chloroform, 278 (sh) (9800), 320 (23,500). Nmr peaks were found between τ 1.9 and 2.7 (9 H aromatic and 1 H vinylic), at 4.68 (1 H methine, doublet, J = 1.7 cps), 7.17 (1 H isopropyl, quintet, J = 6.5 cps), 8.13 (NH, broad singlet), 9.10 (methylisopropyl, doublet, J = 6.5 cps), 9.24 (methylisopropyl doublet, J = 6.5 cps).

Anal. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.91; N, 5.05. Found: C, 82.50; H, 7.04; N, 5.13.

Reaction of 2-[α-(Diisopropylamino)benzyl]-1-indenone with Amines. A. With Morpholine.—To a solution of 0.34 g of **2a** in 50 ml of benzene, 0.92 g of morpholine (10 equiv) were added, at room temperature. The reaction was followed by tlc (ether–petroleum ether, 50–50); only one product was detected. After 2 days, the solvent was evaporated, and the crude product (0.34 g) was analyzed by nmr ($CDCl_3$). The resulting spectrum was superimposable to that of 3-morpholino-2-benzal-1-indanone. The recrystallization of the crude (*n*-hexane + benzene) gave a pale yellow solid (mp 138–139°) having the same melting point, mixture melting point, and R_f as a pure sample of 3-morpholino-2-benzal-1-indanone.[1]

The same experiment was repeated in acetonitrile, with 30 mg of **2a**, 41 mg of morpholine in 10 ml of solvent, at room temperature. The reaction was followed by tlc and found to go to completion after 5 hr. Only one product was detected having the same R_f as **3a**. The evaporation of the solvent gave a solid (28 mg); its nmr spectrum was exactly superimposable with that of **3a**.

In the search for an initial intermediate, we studied (by nmr at −5°) the reaction of 75 mg of **2a** and 24 mg of amine in 0.5 ml of deuteriochloroform. Only **2a**, **3a**, diisopropylamine, and morpholine were detected, and no evidence for an intermediate was found.

B. With Piperidine.—The same reaction was carried out with 0.52 g of **2a** and 1.38 g of piperidine (10 equiv) in 50 ml of benzene at room temperature. After 20 hr, the evaporation of the solvent gave 0.47 g (95%) of a yellow solid which was analyzed by tlc; only one spot was found having the same R_f as **3b**. The nmr spectrum ($CDCl_3$) of the solid was superimposable with that of a pure sample of **3b**. The recrystallization from *n*-hexane gave a solid having the same melting point (141–142°), mixture melting point, and R_f as a pure sample of 3-piperidino-2-benzal-1-indanone.[1]

The same experiment was carried out in acetonitrile with 30 mg of **2a** and 40 mg (5 equiv) of piperidine in 10 ml of solvent. It was found by tlc that the reaction was finished after 10 min. A 26-mg amount of 3-piperidino-2-benzal-1-indanone (92%) was formed and the nmr spectrum ($CDCl_3$) was superimposable with that of a pure sample of **3b**. With 1 equiv of amine in 10 ml of acetonitrile, the reaction went to completion after 2.5 hr.

C. With Pyrrolidine.—The same reaction was carried out with 50 mg of **2a** and 112 mg (10 equiv) of pyrrolidine in 20 ml of benzene at room temperature. The reaction was followed by tlc (ether–petroleum ether, 50:50) until completion (after 5 hr). The solvent was evaporated, and the crude material (containing only one product) was recrystallized in *n*-hexane, mp 122–123°.

(16) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965, p 114.

(17) Melting points were read with a calibrated thermometer. Ultraviolet spectra were determined with a Cary Model 11-MS spectrophotometer. Infrared spectra were measured with a Perkin-Elmer Model 21 instrument. Nmr spectra were determined with a Varian A-60 spectrometer.

(18) The magnetic isopropyl nonequivalence, found in the nmr spectra of this compound and of similar others, is presently under more extensive investigation.

The uv maxima, mμ, in *n*-hexane found at 226, 232 (sh), 272 (sh), 313, 323 (sh) are characteristic of structure **3**.

Anal. Calcd for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 82.81; H, 6.63; N, 5.20.

The preceding reaction was also carried out in acetonitrile with 30 mg of **2a** and 42 mg of pyrrolidine (5 equiv) in 10 ml of solvent, at room temperature. A tlc study showed that the reaction went to completion after 5 min. The crude product obtained by evaporation (27 mg) contained only one compound having the same R_f as **3c**.

D. With *t*-Butylamine.—To a solution of 0.05 g of **2a** in 15 ml of acetonitrile, 0.49 g of *t*-butylamine (40 equiv) was added at room temperature. The reaction was finished after 5 days; the evaporation of the solvent gave an oil which was analyzed by tlc (ether–petroleum ether, 25:75); the presence of **3d** was detected in the crude product. Two recrystallizations of the resulting solid in *n*-hexane gave 28 mg of a pale yellow solid, mp 87.5–88.5°, having the same melting point, mixture melting point, and R_f as a pure sample of 3-(*t*-butylamino)-2-benzal-1-indanone.[1] No reaction was observed in benzene.

Reaction of 2-[α-(*t*-Butylamino)benzyl]-1-indenone with *t*-Butylamine.—To a solution of 100 mg of **2b** in 10 ml of acetonitrile, 75 mg of *t*-butylamine (3 equiv) was added at room temperature. The reaction was followed by tlc. After 26 hr, the indenone **2b** had almost vanished, and the only product was a compound having the same R_f as **3d**. The solvent and the unreacted amine were evaporated and the crude material analyzed by nmr ($CDCl_3$). Only the signals of **2b**,[1] **3d**,[1] and *t*-butylamine were found in the spectrum. The residue, after evaporation of the solvent, was dissolved in *n*-hexane. A yellow solid precipitated on standing in the refrigerator (mp 86°) which was shown by tlc and mixture melting point to be pure **3d**.

Reaction of 2-[α-(Isopropylamino)benzyl]-1-indenone with Isopropylamine.—A 48-mg sample of isopropylamine (3 equiv) was added to a solution of 75 mg of **2c** in 10 ml of chloroform at room temperature. The reaction was followed by tlc (ether–petroleum ether, 30:70). The only product formed had the same R_f as **3e**. After 7 hr, the solvent and the amine were evaporated. The crude material (78 mg of a yellow solid) was analyzed by nmr ($CDCl_3$). The spectrum was almost superimposable with that of **3e** except for a residue of the isopropyl signals of **2c**.

Reactions of 2c with *t*-Butylamine, and 2b with Isopropylamine.—A solution of 75 mg of **2c** and 22 mg of *t*-butylamine in 0.4 ml of deuteriochloroform was introduced in an nmr tube which was sealed and kept at 22°. The reaction was followed by nmr and the only detected compounds were **2c**, **3d**, **3e**, and *t*-butylamine. The signals of **3d** (H methine and H *t*-butyl) appeared first and very slowly; the signals of **3e** appeared later and increased rapidly in intensity. After 20 hr, at the end of the reaction, the ratio **3e**/**3d** was about 3.3. The solvent was evaporated and the residue analyzed by tlc (ether–petroleum ether, 50:50); the results were in agreement with the conclusions of the nmr study.

A similar study was carried out with 75 mg of **2b** and 25 mg of isopropylamine in 0.4 ml of deuteriochloroform at 25°. After 1.6 hr, the reaction was practically finished, and the only detected product was the aminoindanone **3e**, which was also characterized by tlc study.

Exchange Reaction of 3-Piperidino-2-benzal-1-indanone with Morpholine.—A solution of 1 g of **3b** and 3 g of morpholine in 20 ml of benzene was refluxed for 48 hr. After evaporation of the solvent, the remaining oil was dissolved in hot 95% ethanol, and by cooling 0.76 g of pale yellow crystals precipitated, mp 133–136°. The alcoholic filtrate was concentrated and gave a solid which was recrystallized in 95% ethanol; 0.10 g of a pale yellow solid was obtained, mp 136–138°; the mixture melting point of the two solids showed no depression. The product was identified as 3-morpholino-2-benzal-1-indanone (94% yield) by a mixture melting point with an authentic sample, and by uv, ir, and nmr spectra.

The reaction was followed by tlc (ether–petroleum ether, 50:50) and only **3b**, **3c**, and the amine were detected. When the concentration of the amine was increased, another product was formed, characterized by tlc, and found to be 3-morpholino-2-benzyl-1-indenone (**4c**).

II. Isomerization of 3-Amino-2-benzal-1-indanones with Excess of Amine. Preparation of 3-(*t*-Butylamino)-2-benzyl-1-indenone (4a).—A mixture of 0.1 g of **3d** and 5 ml of *t*-butylamine in 5 ml of benzene was allowed to react at room temperature for 73 hr. The evaporation of the solvent gave a red-colored oil which was shown by nmr to be a mixture of 60% of isomerized product **4a** and 40% of starting material.

In another run a solution of 0.18 g of **3d** and 10 ml of *t*-butylamine in 3 ml of benzene was refluxed for 6.5 hr. The reaction was followed by tlc (ether–petroleum ether, 50:50) and only **3d** and **4a** were proved to be present. The solvent and the amine were evaporated and, by addition of a small amount of ether, 0.09 g (50%) of **4a** was formed and separated by filtration: mp 145–147° (methanol); uv maxima, mμ (ε), in methanol were found at 218 (15,500), 255 (sh) (18,200), 264 (20,000), 312 (sh) (1200), 430 (1900); in *n*-hexane at 218 (25,200), 223 (23,000), 255 (26,000), 263 (28,300), 303 (1450), 316 (1100), 320 (1100), 332 (700), 418 (2000); ir absorption (chloroform) was observed at 3450 (NH), 1670 cm^{-1} (C=O); nmr peaks ($CDCl_3$) appeared between τ 2.6 and 2.9 (9 H aromatic), at 5.00 (NH), 6.15 (2 H benzylic, singlet), 8.64 (9 H *t*-butyl).

Anal. Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.52. Found: C, 82.54; H, 7.54; N, 4.81.

A solution of 2.50 g of 2-[α-(*t*-butylamino)benzyl]-1-indenone and 17.5 g of diisopropylamine (20 equiv) in 100 ml of acetonitrile, was heated 20 hr at 100° in a sealed tube. The evaporation of the solvent gave a dark oil which was chromatographed on a column of alumina (eluent: benzene–ether, 50:50). Two fractions were obtained: (1) 0.30 g of an oil containing mainly **2b** and a compound having same R_f as **3d** (tlc: ether–petroleum ether, 55:45); (2) 1.20 g of red oil which was crystallized in ether giving 0.80 g of **4a** (34%), mp 147–148° (*n*-hexane + benzene). This solid has the same melting point, mixture melting point, R_f, and nmr spectrum as an authentic sample of **4a**.

Preparation of 3-Piperidino-2-benzyl-1-indenone (4b).—A solution of 0.34 g of 3-piperidino-2-benzal-1-indanone and 10 ml of piperidine in 5 ml of benzene was refluxed for 3 days. By evaporation of the solvent and the amine, a 0.25-g sample of **4b** (74%) was obtained (after 1 day, the yield was 40%): mp 126–127°; uv maxima, mμ (ε), in methanol were found at 224, (25,000), 275 (23,400), 290 (sh) (11,600), 325 (sh) (2400), 338 (sh) (1400), 460 (4200); in *n*-hexane, 224 (22,200), 265 (19,000), 270 (sh) (17,200), 285 (sh) (8800), 318 (2100) 331 (1400), 430 (3000); ir absorption (chloroform) was observed at 1681 cm^{-1} (C=O); nmr peaks ($CDCl_3$) were found between τ 2.5 and 2.9 (9 H aromatic), at 6.23 (2 H, benzylic), 6.52 (4 H, α to nitrogen), 8.28 (6 H, β and γ to nitrogen).

Anal. Calcd for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.62. Found: C, 83.34; H, 6.79; N, 4.51.

The preceding reaction did not occur at room temperature.

Preparation of 3-Morpholino-2-benzyl-1-indenone (4c).—A mixture of 0.33 g of **3a**, 10 ml of morpholine and 5 ml of benzene was refluxed for 88 hr. The solvent was evaporated and the remaining oil chromatographed on Fluorisil: (1) elution with chloroform–benzene, 20:80, gave 0.165 g of starting material (50%); (2) elution with chloroform–benzene, 80:20, gave 0.044 g of **4c** (15%), mp 125–127° (*n*-hexane + methanol).

In another run, a mixture of 0.60 g of **3a**, 30 ml of morpholine, and 5 ml of xylene was maintained at 110–115° for 70 hr. The reaction mixture was diluted with water, then extracted with benzene, ether, and chloroform. The extracts were dried and the solvent evaporated. The remaining oil was chromatographed on Florisil using benzene as eluent; 0.25 g of **4c** (42%) was obtained after recrystallization from methanol.

The uv maxima, mμ (ε), in methanol were found at 224 (2600), 267 (23,600), 272 (23,400), 290 (sh) (4400), 323 (sh) (2200), 462 (4000); in *n*-hexane, at 223 (21,500), 262 (19,000), 269 (sh) (17,000), 280 (sh) (9500), 318 (2000), 330 (1300), 425 (2600); ir absorption at 1674 cm^{-1} (C=O); nmr peaks were found between τ 2.6 and 2.9 (9 H aromatic), at 6.20 (2 H benzylic, singlet), 6.24 (8 H morpholino).

Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.88; H, 6.28; N, 4.36.

III. Kinetic Procedures.—The reactants were purified as previously reported.[1] Chloroform was passed through a column of neutral alumina twice before being used.

The stability of the starting aminoindenones and resulting aminoindanones were checked under the conditions used during the kinetic studies. These products were found to be stable except for 2-[α-(isopropylamino)benzyl]-1-indenone which decomposed in chloroform, but the reaction rate is very slow (at least during the first 24 hr) and could not compete with the rates of the reactions we have kinetically studied.

The previously reported techniques[1] (uv spectroscopy) were used without modification. The concentrations of the reactant

and product were deduced from the optical densities at three or four wavelengths, and an average of these values was calculated and used in the following expression (a and b are the initial concentrations of the starting ketone and amine, respectively; x is the concentration of the product). The kinetic constants were determined by the least-squares method.

$$1/(b - a) \ln [a(b - x)/b(a - x)]$$

Registry No.—**2a**, 15982-76-0; **2b**, 5387-51-9; **2c**, 16096-94-9; **3b**, 16031-03-1; **3c**, 15982-88-4; **3e**, 16096-36-9; **4a**, 5386-20-9; **4b**, 16003-61-5; **4c**, 16096-39-2.

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Reactions of 1,3-Diphenyl-4-(phenylimino)-2-uretidinone

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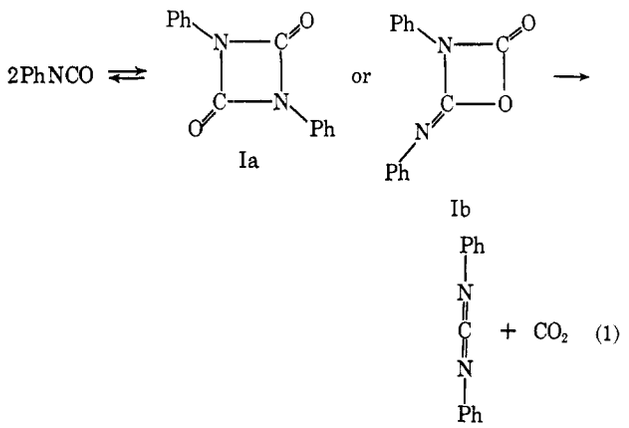
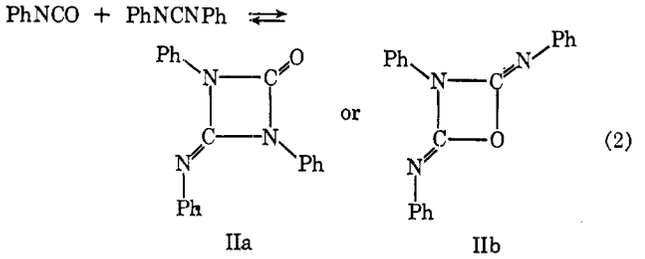
1,3-Diphenyl-4-(phenylimino)-2-uretidinone (IIa) reacts with nucleophiles to give triphenylguanidinecarboxylic acid derivatives. The isolation of the guanidine derivatives confirms the iminouretidinone structure for the isocyanate–carbodiimide adducts. At 80–100°, IIa dissociates reversibly to phenyl isocyanate and diphenylcarbodiimide, with an equilibrium constant of 1.2 at 80° and 4.2 at 100°. The rate constants and activation parameters for the dissociation are described.

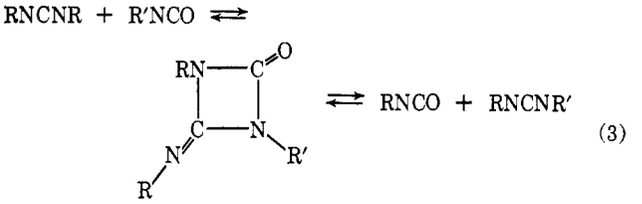
Although cycloaddition reactions of isocyanates, particularly dimerization, have been known for some time, they are incompletely understood and still the object of lively interest.[1] The kinetics of the catalyzed dimerization and dedimerization of phenyl isocyanate have been described recently and the equilibrium nature of the reaction well documented.[2] An uncatalyzed dimerization is also possible, and appears more prevalent with difunctional isocyanates.[3] The structure of the phenyl isocyanate dimer by X-ray diffraction,[4] and the assumed one for all the rest is the symmetrical uretidinedione, Ia, although Ib derives chemical support from the conversion of dimer into carbodiimide with loss of carbon dioxide at 180–200°[5] (eq 1).



A similar uncatalyzed cycloaddition occurs between isocyanate and carbodiimide to give an adduct which by analogy is accorded the iminouretidinone[5] structure, IIa (eq 2).



The ready reversibility of this reaction (eq 3) has prompted its use in the synthesis of mixed carbodiimides.[5] Although either structure (IIa or IIb)



would accommodate the facile interchange reaction, IIa is preferred on the basis of its infrared spectrum, as discussed below.

It was the object of this research to investigate the kinetics of formation and dissociation of II and its chemical reactions. From the results of nucleophilic attack on II, chemical support for structure IIa was obtained.

Results

When equimolar quantities of diphenylcarbodiimide and phenyl isocyanate are heated, with or without cuprous chloride as catalyst,[5] there is obtained II, a white solid, in *ca.* 30% yield. The infrared spectrum of recrystallized II exhibits a carbonyl band at 5.78 μ (1730 cm^{-1}) with a weaker band at 5.88 μ (1700 cm^{-1}). For a four-membered-ring amide carbonyl, the value of 5.73 μ (1745 cm^{-1}) is reported,[6] and the cyclobutaneimine C=N is recorded[7] as 5.76–5.80 μ (1720–1740 cm^{-1}). If one assigns the weaker absorption at 5.88 μ to the C=N group and the 5.78-μ band to the C=O function, then the infrared spectrum is in accord with IIa, and does not support the symmetrical structure IIb.

(1) H. Ulrich, "Cycloaddition Reactions of Heterocumulenes," Academic Press Inc., New York, N. Y., 1967.
(2) R. E. Buckles and L. A. McGrew, *J. Amer. Chem. Soc.*, **88**, 3582 (1966).
(3) J. H. Saunders and R. J. Slocombe, *Chem. Rev.*, **43**, 203 (1948).
(4) C. J. Brown, *J. Chem. Soc.*, 2931 (1955).
(5) W. Neumann and P. Fischer, *Angew. Chem. Intern Ed. Engl.*, **1**, 621 (1962).
(6) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962, p 47.
(7) L. A. Singer and P. D. Bartlett, *Tetrahedron Lett.* 1887 (1964).