Reaction of *cis*-3-Bromo-1,2-dibenzoylpropene with Amines (1a)

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The reaction of *cis*-3-bromo-1,2-dibenzoylpropene (**1**) with amines proceeds by means of a substitution-rearrangement attack to give the 2-(α-aminoacetophenonyl)acrylophenones (**2**). Like similar structures, **2** undergoes further substitution-rearrangement by amines to give 3-benzoyl-5-phenylpyrroles (**5**) and an enaminoketone, α-acetophenonyl-β-aminoacrylophenone (**3**). Competitive with substitution-rearrangement, amine addition to **2** followed by loss of hydrogen and then water leads to formation of the 3-benzoyl-4-amino-5-phenylpyrroles (**4**). The enaminoketones (**3**) by contrast with **2** are quite stable. Structure **2** when in polar solvents or in the presence of amines undergoes substitution-rearrangement to give **3**, which can be induced to give the pyrroles (**5**) when exposed to acid conditions. When neat or in solvents of low polarity, **2** undergoes intermolecular substitution-rearrangement-dehydration to give **5** almost exclusively.

A novel addition reaction of 3-benzoyl-5-phenylfuran involving attack by isopropyl- or cyclohexylamine provides a quantitative method of synthesizing the appropriate *N*-substituted examples of **3** and an efficient method of deriving the corresponding pyrroles (**5**).

Introduction.

In continuation of our investigation of the chemistry involved in the reactions of carboallyl halides with primary amines, we have studied the addition of amines to the highly mobile β,γ-diketoallyl system, *cis*-3-bromo-1,2-dibenzoylpropene (**1**). Previous studies of the β-ketoallyl system, *trans*-α-bromomethylchalcone (2,3), and the γ, ketoallyl system, *trans*-β-bromomethylchalcone (4), have been made in this laboratory. It was found that the β-ketoallyl system in general underwent amine attack by a variant SN2′ displacement and not by a Michael attack, giving a diaminoketone, followed by a Michael elimination (2,3). The resulting substitution-rearrangement product, an acrylophenone, could then undergo a second substitution-rearrangement by either an amine attack or by a "self-rearrangement" to give the β-ketoallylamine (2abc,3). This self-rearrangement is indicated by kinetic data to be an intermolecular process and may proceed by a bimolecular rearrangement or as a chain reaction involving the release of amine (3). The γ-ketoallyl system, lacking the β-ketone "electron sink" which facilitates the SN2′ displacement, probably undergoes amine attack in a direct SN2 fashion (4). In **1**, possessing both of these systems, our study with amines shows the expected attack by a substitution-rearrangement pathway typical of the β-ketoallyl system followed by either a second substitution-rearrangement or addition of an amine to give three types of products. Like the substitution-rearrangements observed for the other β-ketoallyl systems, the rates of these competitive reactions are very sensitive to space-demand of the amine (*e.g.* number of α-substituents on N-R) and the polarity of the solvent (2abd).

In previous studies by Bailey and Lutz, the reaction of **1** and other similar compounds with hydrogen, morpholine, alcohol, water and hydrogen bromide was found to give various addition, cyclization and displacement products (6,7). Both **1** and *cis*-3-morpholino-1,2-dibenzoylpropene (7) undergo cyclization to 3-benzoyl-5-phenylfuran by what is suggested to be a 1,5-enolization followed either by a direct elimination of amines or by formation of an "inner salt" which might represent the point at which morpholine or bromine is eliminated (5,7). When **1** was allowed to react with morpholine, *trans*-3-morpholino-1,2-dibenzoylpropene was quickly formed and like the *cis*-isomer also cyclized but much more readily (7). The two authors did not suggest any mechanism for formation of this *trans* compound from **1**.

Results.

The preparation of **1** is readily accomplished in reasonable yield by bromomethylation of 2,5-diphenylfuran to give the corresponding 3-bromomethyl compound. Nitric acid oxidation of the later then gives exclusively the *cis*-product, **1**, (7,8).

When **1** was allowed to react with primary amines (*t*-butyl-, isopropyl- and cyclohexylamine, respectively) the

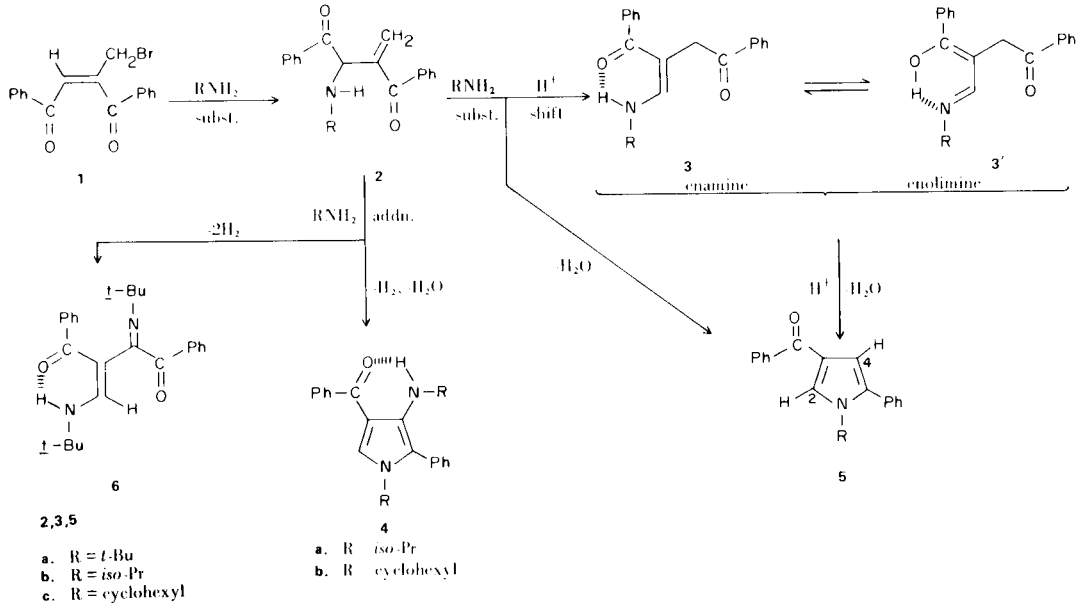

Figure 1. Products isolated from the reaction of *cis*-3-bromo-1,2-dibenzoylpropene (1) with amines.

major products were a 3-benzoyl-5-phenylpyrrole (**5a**, **5b**, **5c**) and a 4-amino-3-benzoyl-5-phenylpyrrole (**4a**, **4b**). With *t*-butylamine there was no aminopyrrole (**4**) observed in the reaction mixture with **5a**. After repeated crystallization of **5a** from the reaction mixture residue, a trace (2%) of **6**, an imino-enaminoketone, was isolated. Compound **8** (*cf.* Figure 9), very similar to **6**, was obtained by reaction of **7** with morpholine in *n*-pentane. Compound **7** was synthesized in a fashion analogous to the preparation reported for *cis*-3-morpholine-1,2-dibenzoylpropene. With isopropylamine the two major products, **5b** and **4a**, were observed in the nmr spectrum of the reaction mixture in a ratio of 1:1, respectively. This ratio was observed to be 1:2 in the case of cyclohexylamine. Thus it appears that the space demand of the amine is a regulating factor in determining the ratio of amine addition to **1** versus substitution-rearrangement.

A product similar to **5** was observed in this laboratory by Rodebaugh and Cromwell in 1967 (9). When *trans*-β-bromomethylchalcone was allowed to react with amines, 2,4-diphenylpyrroles were directly isolated. No aminopyrroles were detected.

It was found in nmr spectra taken at certain time intervals during the course of a reaction of **1** with either *t*-butyl- or cyclohexylamine (in both chloroform and in ether) that one isolatable intermediary (**2**) and one other product (**3**) were present. The intermediate **2**, a 2-(α-aminoacetophenonyl)acrylophenone, is the direct result of an amine substitution-rearrangement on **1** and then must undergo either a second amine substitution-rearrangement or intermolecular substitution-rearrangement with another molecule of **2** to give the enaminoketone **3**. This transformation was observed to be more facile in chloroform than in ether, typical of these systems (2ad). In the reaction of **1** with *t*-butylamine in chloroform only a feeble appearance of **2a** was observed due to rapid conversion of **2a** to **3a**. In ether, both **2a** and **3a** were immediately observed, reaching equal population and then **2a** rapidly disappeared leaving **3a** and **5a**. Though conversion of **2a** or **3a** to **5a** in either solvent was never complete, a much higher proportion of **5a** was observed in chloroform. In the reaction of **1** with cyclohexylamine in chloroform both **2c** and **3c** could be observed (the concentration of **3c** approximately three times that of **2c**) along with **5c** but no **4b** could be observed. In ether, both **2c** and **3c** were observed first and in nearly equal quantity, then **5c** and **4b** formed in a 1:2 ratio, simultaneously. This latter reaction was completed in one-half hour, with nearly complete conversion to **5c** and **4b**. This completeness of conversion observed with either isopropyl- or cyclohexylamine allowed us to contrast the ratios of **5** to **4** under varying conditions with either amine.

It is a competition in **2** between substitution-rearrangement to **3** and **5** and 1,4-addition of amine that determines the ratio of products. This competition is controlled on the one hand by polarity of the solvent medium and on the other hand by the space-demand of the attacking amine. Cyclohexylamine and isopropylamine having similar polarity, it is obvious that addition of the less space-demanding cyclohexylamine competes better against substitution-rearrangement of **2** than does isopropylamine.

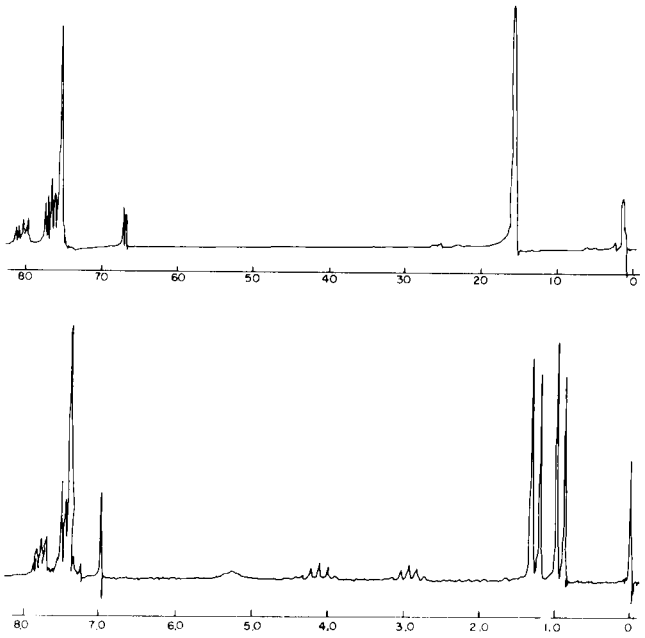

Figure 2. (a) 60 MHz proton nmr spectrum of compound **4a** in chloroform-D. (b) 60 MHz proton spectrum of compound **5a** in chloroform-D.

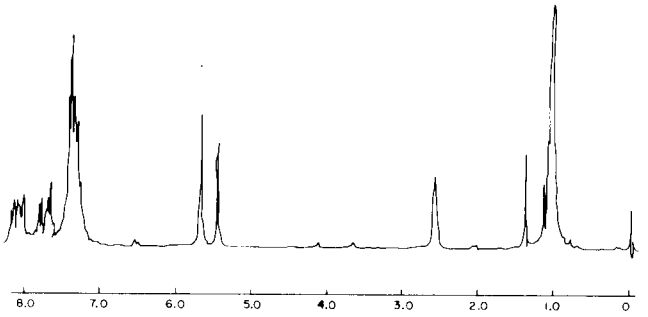

Figure 3. 60 MHz proton nmr spectrum of compound **2a** in chloroform-D.

This competition quite adequately explains the effects of amine concentration and solvent. Amine concentration had little effect on the observed ratios of **4** and **5**; both paths (**2** to **3** and **2** to **4**) were apparently equally facilitated as amine concentration increased (*i.e.* likelihood of amine attack on **2** increased in proportion to polarity promoting substitution-rearrangement of **2** to **3**). As was noted in the earlier discussion, conversion of **2** to **3** in chloroform was more facile than in ether, regardless of amine concentrations due to its greater polarity and thus a lower yield of **4** was observed than in ether solvent.

All three examples of **2**(a,b,c) could be isolated but **2a** was the most stable and could be isolated in higher yield than **2b** or **2c**. Only **3a** was isolated directly from reaction of **1** and primary amines but **3b** and **3c** could be prepared efficiently by reaction of the appropriate amines with 3-benzoyl-5-phenylfuran (*cf.* Figure 7). No reaction was observed between this furan and *t*-butylamine.

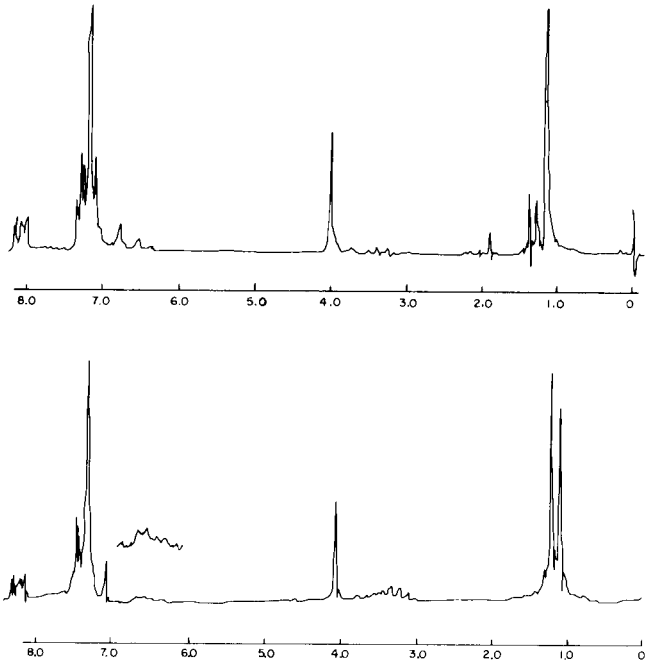

Figure 4. (a) 60 MHz proton nmr spectrum of compound **3a** in chloroform-D. (b) 60 MHz proton nmr spectrum of compound **3b** in chloroform-D.

The nmr data is presented in Table I and key spectra are shown in Figures 2-4. The nmr signals for the ring protons H2 and H4 in **5** are in reverse order to those observed for the 2,4-diphenylpyrroles (9). Indications are that the benzoyl group in **5** and **4** is oriented specifically as drawn in Figure 1. In both **6** and **8**, the vinyl proton is approximately 1 ppm downfield from H2 observed for **5** and **4** and 0.6 ppm downfield from the vinyl proton in **3a**, We believe this low field chemical shift is due to adoption of the specific configuration-conformation drawn for **6** and **8** in Figures 1 and 9. In the nmr spectra of **2**, the two characteristic vinyl proton signals were observed (5.8 and 5.6 ppm) and were overlapped by the methine proton signal at 5.7 ppm. Each set of *ortho*-proton signals for the two phenyl groups (benzoyl) in **2** was observed separately downfield from the meta and para protons. All the other compounds in addition to one set of benzoyl signals contained a phenyl absorption which was observed as a singlet at 7.4 ppm.

In the infrared spectra, the expected vinylogous amide carbonyl stretching frequency, 1640-1625 cm^{-1}, is readily

Table 1

Proton nmr Data Recorded at 60 MHz in Chloroform Solvent.
Frequencies are Expressed in ppm Downfield from TMS.

Cpd.	Aromatic	sp^2	N-H	Methylene	Methine	N-R Groups
5a	7.90 (m,2) 7.53 (m,4) 7.40 (s,5)	6.57 (d,1) (1)	-	-	-	1.43 (s,9)
5b	7.92 (") 7.47 (") 7.42 (")	6.63 (") (1)	-	-	4.53 (h) (2)	1.43 (d,6) (2)
5c	7.88 (") 7.50 (") 7.38 (")	6.66 (") (1)	-	-	3.92 (b)	1.58 (b,11)
4a	7.80 (") 7.50 (m,3) 7.40 (")	7.02 (s,1)	5.50	-	4.13 (h) (2) 2.95 (h) (2)	1.25 (d,6) (2) 0.92 (d,6) (2)
4b	7.75 (") 7.47 (") 7.40 (")	6.97 (")	5.18	-	3.53 (b) 2.43 (b)	1.25 (b,22)
6	7.98 (") 7.45 (") 7.36 (")	7.88 (")	(a)	-	-	1.26 (s,9) 1.23 (s,9)
8	7.92 (") 7.45 (") 7.45 (")	7.85 (d,1) (3)	11.15 (d) (3)	-	-	1.28 (")
2a	8.12 (") 7.75 (m,2) 7.38 (m,6)	5.69 (s,1) 5.45 (s,1)	2.58	5.70 (s,1)	-	1.07 (s,9)
2b	8.08 (") 7.72 (") 7.48 (")	5.89 (") 5.63 (")	3.50	5.72 (")	-	1.17 (d,6) (2)
2c	(a) (a)	5.81 (") 5.65 (")	3.17	5.68 (")	-	(a)
3a	8.08 (") 7.25 (m,3) 7.18 (s,5)	7.27 (d,1) (3)	6.68 (dd) (2,3)	4.02 (s)	-	1.15 (s,9)
3b	8.08 (") 7.33 (") 7.16 (")	7.10 (") (3)	6.45 (dd) (2,3)	4.00 (")	2.88 (o) (2)	1.08 (d,6) (2)
3c	8.08 (") 7.33 (") 7.20 (")	7.10 (") (3)	6.48 (dd) (2,3)	4.02 (")	2.75 (b)	1.25 (b,11)

s = singlet, d = doublet, m = multiplet, h = heptet, o = octet, b = broad absorption. (a) obscured peak (1) J = 2 cps (2) J = 7 cps (3) J = 14 cps.

observed in compounds **3**, **4**, **5**, **6**, and **8** (*cf.* Table 2). The N-H stretching frequencies in **3** and **4** indicate the intramolecular hydrogen-bonding (17) and different solvents and dilution studies showed little effect on the frequency of this absorption.

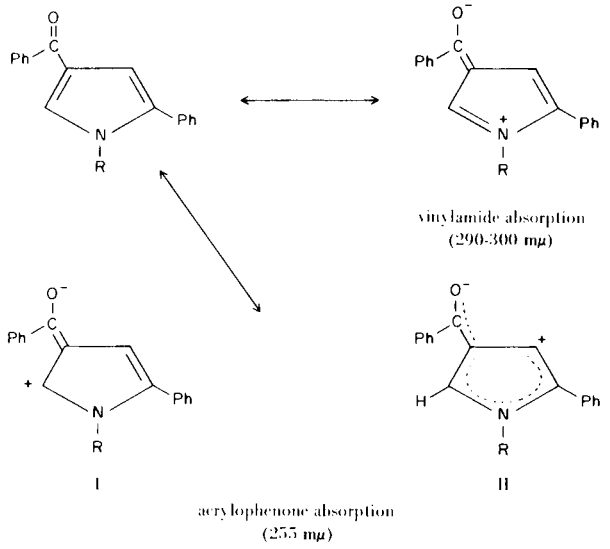

Figure 5. Resonance forms of compound **5**.

Table 2

Infrared Absorptions (Carbon Tetrachloride)

Compound	N-H (cm^{-1})	Carbonyl Region (cm^{-1})		
2a	3280	1685	1660	
3a	3300, 3240 (s)		1660	1635
3b	3290, 3200 (s)		1660	1635
3c	3300, 3230 (s)		1660	1635
6	N.A. (a)	1680		1630
8	N.A.	1675		1640,1625
5a	-----			1635
5b	-----			1635
5c	-----			1635
4a	3330			1625
4b	3335			1617
9	-----			1640
10	-----			1635

(a) Absorption not observed - very broad.

The main absorption observed in the uv spectra of **4** may be attributed to vinylamide delocalization (*ca.* λ max 290 mμ). A second, much less dominent, absorption observed as a shoulder at 350 mμ may be attributed to a four-charge-center resonance interaction (*cf.* Figure 6). The yellow color of the aminopyrrole is probably derived from this latter band. In the uv spectra of **5** there is one strong band in the 250-255 mμ area and a small shoulder corresponding to vinylamide delocalization at 300 mμ. The strong band may be attributed to acrylophenone delocalization (*cf.* Figure 5). Compounds **3**, **6** and **8** show the expected vinylamide delocalization.

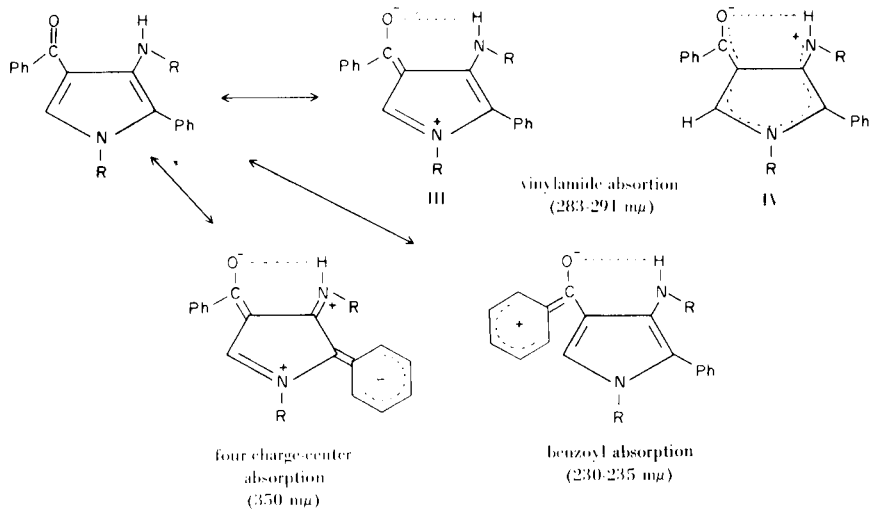

Figure 6. Resonance forms of compound **4**.

Table 3

Ultraviolet Absorptions.

Compounds	Solvent	λ max (ε) (a)
5a	Methanol	252(14,900) 300(s) (6,800)
5b	"	253(22,600) 300(s) (7,700)
5c	"	255(15,000) 300(s) (5,100)
4a	"	235(15,300) 288 (21,000) 350(s) (7,800)
4b	"	233(15,600) 289 (20,100) 350(s) (4,300)
6	"	242(18,400) 300 (18,900)
8	"	250(14,800) 295 (16,000)
2a	"	249(17,200)
3a	"	243(15,800) 308 (15,600)
3b	"	246(18,100) 310 (16,000)
3c	"	240(22,100) 308 (20,000)
10	"	243(16,800) 280 (14,400)
9	"	255(16,800) 272(s) (12,900)
5a	Isooctane	248(15,700) 290(s) (6,100)
5b	"	253(20,000)
5c	"	255(20,300)
4a	"	235(14,500) 283 (15,500)
4b	"	235(26,800) 283 (24,600)
6	"	242(18,200) 283(s) (12,400)

(a) Frequency reported in mμ.

Discussion.

In general, 3-carbopyrroles must be prepared indirectly, being formed by ring-closure of a suitable intermediate or by more devious routes (10). Aminopyrroles are usually very unstable and though 2- and 3-aminopyrrole are unknown, those aminopyrroles containing electron-attracting groups (phenyl, benzoyl, cyano, etc.) are quite stable and in general rather strong bases (11, 12, 13, 14). Very recently, a novel preparation for β-aminopyrroles from enaminonitriles has been reported (15). Pyrrole (**4**) is unique in that it contains, with respect to the ring nitrogen, both a β-carbo group and a β-amino group. This arrangement has a strong electronic effect on the pyrrole nucleus. The properties of functional groups on pyrroles are a

consequence of the "electron-rich" nature of the pyrrole nucleus (13) and the variations in the whole electronic structure, as we have witnessed by uv spectra, do not depend on the ring nitrogen atom but are related to the functional groups and their positions (16). That acrylophenone delocalization (*cf.* Figure 5) in **5** is much more favored than the expected vinylamide delocalization is surprising. Of two modes possibly associated with this acrylophenone delocalization, mode I is illogical and it is more likely that this acrylophenone delocalization is best described by mode II. The fact that **2** shows a single acrylophenone band as its uv absorption so similar to that observed in the pyrrole product is another indication that this band is **5** is associated with mode II. Mode I is possible, of course, in **3**, **6**, and **8** but the expected vinylamide delocalization is observed in these compounds. The bands in the uv spectra of **4** show a pronounced increase in the vinylamide absorption with introduction of an amino group in the β-position. Analogous to mode II in **5**, one can consider mode IV (*cf.* Figure 6) describing the very strong vinylamide delocalization introduced by the presence of the β-amino group. There is no acrylophenone band observed in the aminopyrroles as observed in **5**. As expected, neither a methiodide (**9**) or hydrochloride salt of **4** exhibited a vinylamide absorption at all, thus indicative that it is indeed the β-amino group alone that is responsible for nearly all of this delocalization, only possible through mode IV. The data thus observed is consistent with the general conclusion that it is the functional groups on the pyrrole nucleus that mainly determine the electronic structure.

Enaminoketones have been extensively discussed in the literature and ir, uv, and nmr studies of various types of these compounds have indicated the sites of protonation or alkylation and have demonstrated the *cis-trans* and enamine-enolimine tautomerism which these compounds can exhibit (17, 18). The enaminoketone structure of **3** is revealed by the coupling observed in the nmr spectra. In 100 MHz nmr spectra of **3b** the olefinic proton absorption (partly obscured at 60 MHz) is clearly a doublet (J = 14 cps) with the expected coupling constant for an α-amino vinyl proton oriented *trans* to the N-H proton (19); =C(H)-N(H)-R. Correspondingly, the N-H protons in **3a,b,c** and **8** (N-H could not be located in **6**) were observed to be split by a coupling constant of 14 Hz. In addition, the N-H protons in **3b** and **3c** were also coupled to the methine carbon of the N-R group (J = 7 cps), thus a doublet of doublets. At 100 MHz, the methine carbon absorption in **3b** was clearly observed to be an octet. Irradiation of the N-H proton in **3b** caused the octet to collapse to a sextet (easily confirmed by the change in intensity distribution) and irradiation of the methine absorption caused the N-H absorption to collapse to a doublet (J = 14 cps). The relatively low chemical

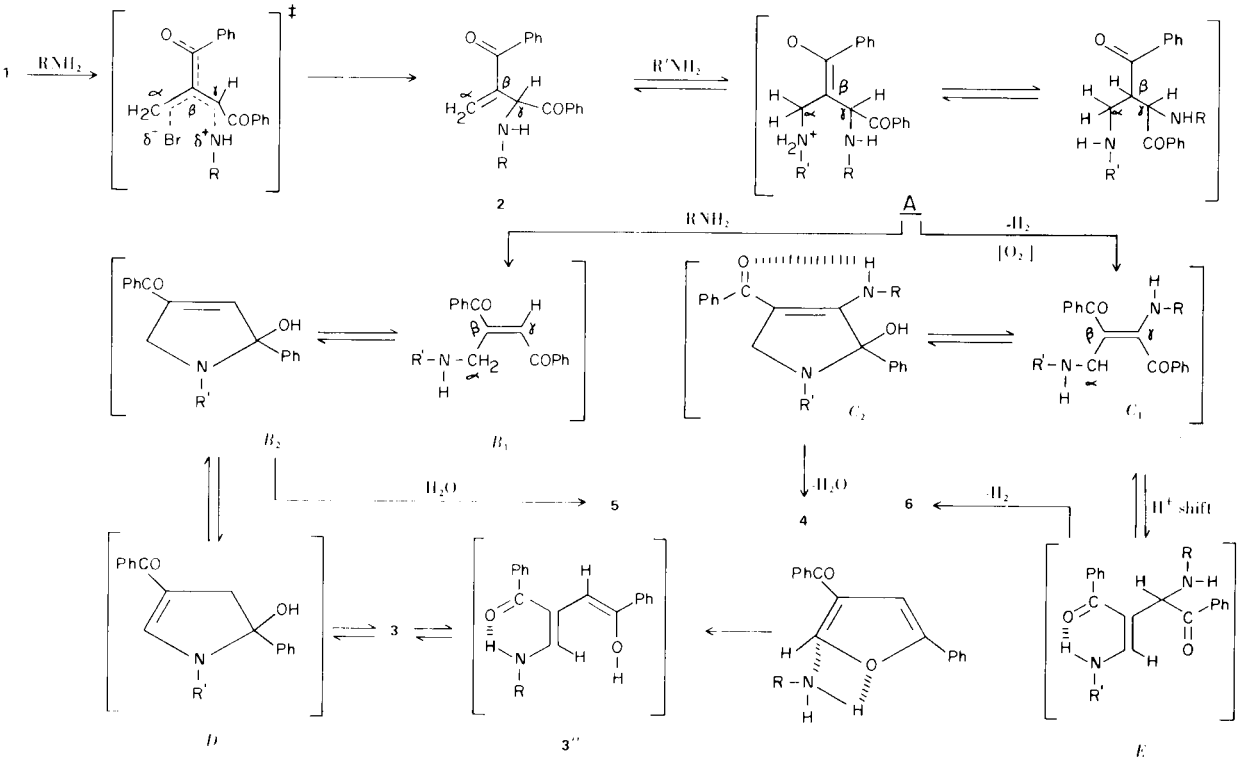

Figure 7. Mechanistic pathway for formation of **3**, **4**, **5** and **6**.

shifts observed for the N-H protons in **3** and **8** in addition to the observed singlet for the chelating benzoyl group leads us to conclude that in **3**, **6** and **8** the enamine-enolimine tautomerization (*cf.* Figure 1) is very fast and on the nmr time scale the two tautomers cannot be distinguished. It is interesting to note in passing that the acetophenonyl group does not appear to be enolized.

Considering formation of **2**, we expect a transition state involving amine attack on **1** (*cf.* Figure 7) at the γ-carbon synchronous with the carbon-halogen bond breaking in which much of the developing negative charge is accepted by the β-carbonyl group oxygen atom (2,3). The very high field N-H signal in **2** at 2.5-3.5 ppm precludes the possibility that the amino group proton is associated in any way with the β-ketone function (note the N-H at 6.5 ppm in **3**) and thus the conformation of **2** prior to amine attack as shown in Figure 7 is likely. Undergoing further attack by another molecule of amine as shown, **2** might be expected to give *A* and at this point intermediates *B* and *C* are formed. We suggest the regulating factor in determining the ratio of *B* and *C* from *A* is the space-demand of the attacking amine. The formation of addition product *A* (no analogous addition products were observed before with either the β- or γ-ketoallyl systems) would make the β,γ-diketoallyl system unique. The presence of addition product *A* would indicate the greater strength of the γ-carbon to nitrogen bond caused by the electron withdrawing inductive effect of the γ-ketone function. Thus, unless the two amino groups in *A* are bulky, proton transfer takes place on the β-carbon in *A* and there is a loss of hydrogen to give intermediates $C_1 \rightleftharpoons C_2$ rather than a proton transfer to the γ-amino nitrogen atom followed by elimination of an amine moiety to give intermediates $B_1 \rightleftharpoons B_2$. That no products containing two amine moieties were detected with the γ-ketoallyl system is further evidence that substitution in that system is direct SN2 and no amine attack at the γ-carbon takes place (4,9).

It is suggested that *B* is first formed as a *trans*-amino analogue of **1** (as indicated) and then immediately ring-chain tautomerizes to the Δ^3-pyrroline form (B_2). The *cis*-isomer of B_1 (*cf.* Figure 9), *cis*-3-*t*-butylamino-1,2-dibenzoylpropene (**7**), has been prepared in this laboratory for the first time and in the presence of amine in ether only slowly undergoes attack (*ca.* one week). Further, neither this *cis*-isomer (**7**) nor especially the *trans*-3-morpholino-1,2-dibenzoylpropene (which can not cyclize to B_2) undergo rapid tautomerization to an enaminoketone in amine solution. Thus, the proposed *trans*-isomer B_1 must first and almost immediately cyclize to B_2 and only then either lose water or tautomerize to **3**. The necessary cyclization prior to tautomerization would destroy the dibenzoylethylene conjugated system, apparently a requirement before tautomerization to the vinylamide system can take place.

The Δ^3-pyrroline intermediate B_2 thus determines the ratio of **3** to **5**. In polar solvents or in the presence of amines, tautomerization to *D*, the Δ^2-pyrroline (extention of the conjugated system), would be very facile and subsequent ring opening (the basicity of the nitrogen atom now considerably weakened) followed by *trans* ⇌ *cis* isomerization would lead to **3**. In solvents of low polarity or neat, 1,4-loss of water from **2** by way of B_2 to give the pyrrole product (**5**) is more facile. The pure oil **2a** has been observed to give **5** in nearly quantitative yield (90-95%) in less than 24 hours whereas in amine solution formation of **3** (70-80%) is more facile. The Δ^3-2-hydroxypyrroline type structure exhibited in B_2 (and C_2) has been observed by others to undergo 1,4-loss of water (20) and our observation of **2a** (neat) going to **5a** implies the formation of Δ^3-pyrroline intermediate B_2 followed by 1,4-loss of water. It is not expected that B_2 has a very long life-time and it is doubtful that B_2 undergoes attack by amines. Further evidence for this arguement will be given in a forthcoming publication.

As a working mechanism for the alternative preparation of **3**, addition of amine to 3-benzoyl-5-phenylfuran, we suggest a concerted addition of amine as shown in Figure 7 to give directly **3**″, the enol-isomer of **3**. The suggested mechanism is simply the reverse of furan formation from *trans*-3-morpholino-1,2-dibenzoylpropene (*cf.* Introduction).

Amine addition on **2** and subsequent formation of **4** takes place very rapidly. The suggested intermediates C_1 and C_2 (*cf.* Figure 7) could not be positively detected. We suggest that loss of hydrogen from *A* occurs first forming intermediate C_1 which (like B_1) then ring-closes to give C_2. There are several reasons for this assumption. Loss of hydrogen in this manner from certain α-aminoketones has already been demonstrated to be a facile process (21). Also, if a pyrrolidine ring structure *F* (*cf.* Figure 8) had formed prior to loss of hydrogen, we might expect that loss of water could occur first, a process we tend to dismiss in view of chemical evidence (see later discussion). Also, loss of hydrogen from *F* might be expected to occur across either the 2,3- or the 3,4-bond with equal facility. Loss of hydrogen across the 3,4-bond would give the chelated intermediate *C* but statistically it is more probable that loss of hydrogen would occur across the 2,3-bond in *F* to afford the Δ^2-isomer of C_2 (note similarity to *D*). We would expect such a Δ^2-isomer of C_2 to ring-open to give an enaminoketone *E* (note similarity to **3**) followed by further loss of hydrogen to give a structure of the type **6**. No **6** was detected in the reaction of **1** with either isopropyl- or cyclohexylamine. Consistent with this fact, we would not expect C_2 to

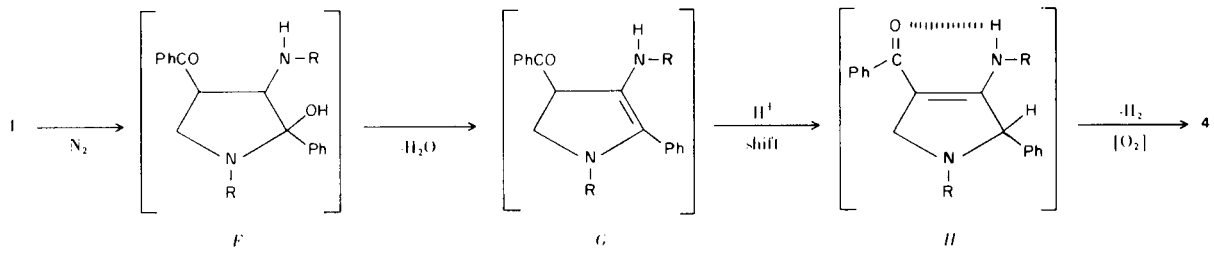

Figure 8. Mechanistic pathway for formation of **4** under nitrogen atmosphere.

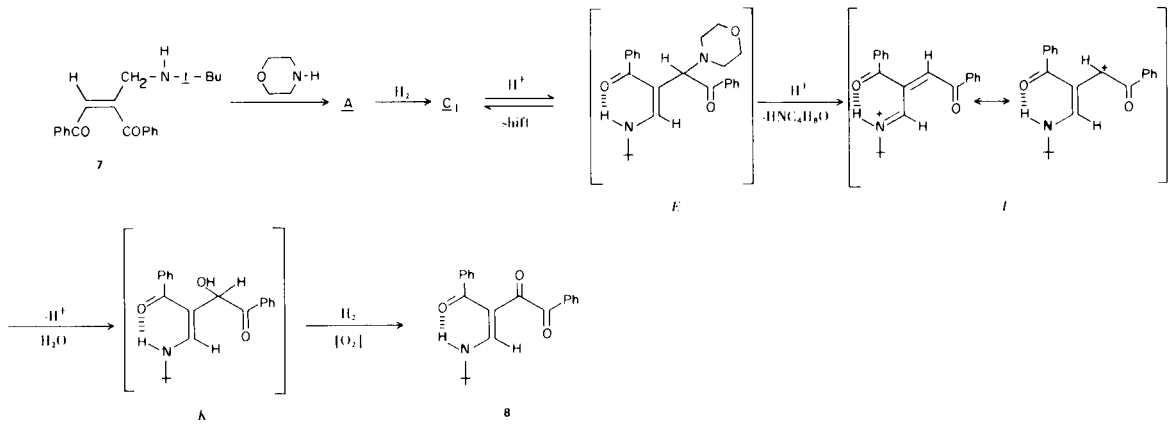

Figure 9. Mechanistic pathway for formation of **8** from **7**.

readily tautomerize to the Δ^2-isomer as in the case of B_2 on account of the vinylamide conjugation already present in C_2. In the case of *t*-butylamine, we suggest that steric factors introduced by the presence of two *t*-butylamine moieties preclude ring-closure to C_2 and that C_1 might then slowly tautomerize to *E* followed by loss of hydrogen to give **6**. Thus, by what appear to be parallel pathways B_2 and C_2 undergo 1,4-loss of water to give the corresponding pyrroles.

To further test our mechanism, some reactions were carried out under a nitrogen atmosphere to inhibit loss of hydrogen by auto-oxidation. Reactions were attempted using both cyclohexyl- and isopropylamine (20 equivalents) in hexane rather than ether to permit clear observation of the nmr signals in the reaction mixture. Signals corresponding to two new intermediates were observed. The first intermediate was stable for only a short time under nitrogen and gave rise to a second intermediate which was relatively air-stable. This second intermediate was observed over several days to slowly form the aminopyrrole on exposure to air and we could not isolate it from the latter. However, from nmr signals in the residue, it is suspected that this second intermediate is *H*. Where R = *iso*propyl, the N-H proton signal for intermediate *H* is at 10.23 ppm (J = 7-8 ppm) characteristic of the chelated enaminoketone. In addition, a slightly broadened signal occurs at 5.03 ppm (1H) and a complex AB quartet centered at 4.0 ppm (2H). These latter two absorptions are assigned to the ring methine and methylene protons, respectively, and are similar in appearance and chemical shift to the corresponding ring proton signals in 4-methyl-2,5-diphenyl-4-cyano-Δ^1-pyrroline (22). The intermediate precursor to *H* would be the Δ^2-isomer, *G*. The fact that these two new intermediates were observed at all is evidence that the process of hydrogen loss was inhibited under nitrogen atmosphere and loss of water must have occured first to give a new air-stable product, not previously observed in reactions exposed to the air. Further evidence will be presented in a forthcoming publication.

A working mechanism for formation of **8** is shown in Figure 9. The *t*-butylamine function in **7** is not expected to be as good a leaving group as bromine. Thus **1** adds morpholine to give *A* which then dehydrogenates to C_1. Again as in the formation of **6**, steric factors might preclude ring-closure to C_2 and tautomerization to *E* might be expected. Not able to lose hydrogen to give a structure of type **6**, further treatment of *E* with aqueous 3 *N* hydrochloric acid could then have resulted in transformation to *K*, through structure *I*, followed by loss of hydrogen giving the final product **8**.

We are continuing our investigation into the unusual and interesting chemistry of this very mobile and complex system and its related compounds.

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EXPERIMENTAL

Melting points were determined with a Mel-temp capillary tube melting point apparatus and are uncorrected. The melting points of some of the compounds were dependent upon the rate at which the sample was heated and were generally determined by inserting the sample into the apparatus which was preheated to 30° below the expected melting point.

Elemental analyses were performed by the Micro Tech Laboratory in Skokie, Illinois.

The nmr spectra were routinely recorded on a 60 MHz Varian A-60d instrument and the 100 MHz nmr spectrum of **3a** on a Varian XL-100 instrument. Ir spectra were obtained on a Perkin-Elmer model 237 grating infrared spectrophotometer. Uv spectra were recorded on a Cary 14 recording spectrophotometer.

I. Reaction of **1** with Amines.

General Method of Procedure.

The resulting reaction mixtures as described in each preparation were stirred at room temperature for 2.5 hours during which time the amine hydrobromide salt precipitated. The reaction mixture was then filtered, washed several times with water and the aminopyrrole (**4**) extracted with aqueous 3 *N* hydrochloric acid. The mother liquor was then washed with water, dried over sodium sulfate and evaporated under reduced pressure. The residue was crystallized from 95% ethanol to give the pyrrole product (**5**). The acid extract was neutralized with sodium carbonate and extracted with ether. The extract was treated in analogous manner to the mother liquor to yield the aminopyrrole (**4**).

A. *t*-Butylamine. Preparation of 1-*t*-Butyl-3-benzoyl-5-phenylpyrrole (**5a**) and α-(1-*t*-Butyliminoacetophenonyl)-β-*t*-butylaminoacrylophenone (**6**).

In 500 ml. of ether was dissolved 13.4 g. of **1** and 83.7 ml. (20 equivalents) of *t*-butylamine were added. After following the general method of procedure, 5.0 g. of **5a** was precipitated from the mother liquor and an additional 1.46 g. from the acid extract for a total of 6.46 g. (52%). Of this, 5.0 g. was recrystallized from ethanol to give 4.25 g. of light ivory needles, m.p. 174-175°.

From a reaction involving 50.0 g. of **1** was obtained from the residue, after many repeated crystallizations of **5a**, a total of 2.18 g. of crude material containing **6**, m.p. 154-160°. The crude material was recrystallized from ethanol to yield a precipitate of two crystalline compounds which were separated by heating the precipitate in chloroform. Only **6** was soluble and separated from an undentified material, 170 m.g., m.p. 217-220° dec. From chloroform was precipitated 1.0 g. (2.6%) of **6**, light yellow granular crystals; m.p. 171-172°.

For **5a**: *Anal.* Calcd. for $C_{21}H_{21}ON$ (303.43): C, 83.12; H, 6.99; N, 4.62. Found: C, 83.43; H, 7.03; N, 4.50.

For **6**: *Anal.* Calcd. for $C_{25}H_{30}N_2O_2$(390.51): C, 76.89; H, 7.74; N, 7.17. Found: C, 76.73; H, 7.93; N, 7.13.

B. Isopropylamine. Preparation of 1-Isopropyl-3-benzoyl-5-phenylpyrrole (**5b**) and 1-Isopropyl-3-benzoyl-4-isopropylamino-5-phenylpyrrole (**4a**).

In 250 ml. of ether was dissolved 5.0 g. of **1** and 26 ml. (20 cuqivalents) of isopropylamine was added. After following the general method of procedure, 1.07 g. of crude **5b** was isolated from the mother liquor which was recrystallized from ethanol to give 0.36 g. of light ivory needles, m.p. 107-108°. From the acid extract was obtained 2.85 g. of **4a** which was recrystallized from ethanol to give 2.50 g. of the fine yellow granular crystals, m.p. 111-112°. The aminopyrrole (**4a**) decomposes in ethanol solution after several days at room temperature.

For **5b**: *Anal.* Calcd. for $C_{20}H_{19}NO$ (289.36): C, 83.10; H, 6.62; N, 4.84. Found: C, 83.08; H, 6.59; N, 4.79.

For **4a**: *Anal.* Calcd. for $C_{23}H_{26}ON_2$ (346.46): C, 79.73; H, 7.56; N, 8.09. Found: C, 79.64; H, 7.61; N, 7.92.

C. Cyclohexylamine. Preparation of 1-Cyclohexyl-3-benzoyl-5-phenylpyrrole (**5c**) and 1-Cyclohexyl-3-benzoyl-4-cyclohexylamino-5-phenylpyrrole (**4b**).

In 600 ml. of ether was dissolved 25.0 g. of **1** and 184 ml. (20 equivalents) of cyclohexylamine was added. After following the general method of procedure 4.49 g. of crude **5c** was isolated from the mother liquor of which 3.57 g. was recrystallized from ethanol to give 1.24 g., *cf.* light ivory needles, m.p. 114-115°. The yellow amorphous **4b** was precipitated from the acid extract, 6.7 g. Recrystallization provided fine silky yellow needles, m.p. 165-167°.

The picrate of **4b** was prepared in the usual manner. To a saturated solution of picric acid in ethanol (7.5 ml.) was added 0.20 g. of **4b** in 7.5 ml. of 95% ethanol and the resulting solution heated to boiling and allowed to slowly crystallize under refrigeration. The picrate (**4bP**) was obtained as lemon yellow granular crystals, 0.16 g. (52%) melting at 190-194°. The material was recrystallized from ethanol, 0.14 g., m.p. 192-193°.

For **5c**: *Anal.* Calcd. for $C_{23}H_{23}NO$ (329.42): C, 83.85; H, 7.04; N, 4.25. Found: C, 83.89; H, 7.14; N, 4.19.

For **4b**: ir (P-E Model 621, carbon tetrachloride): 3335 (s), 3030 (s), 3010 (s), 2945 (l), 2860 (m), 1617 (l), 1500 (l), 1480 (m), 1450 (m), 1380 (s), 1350 (m), 1310 (s), 1250 (s), 1215 (s), 1160 and 1130 (d,s), 1090 (s), 1070 (s), 1025 (s), 890 (m), 600 (m).

Anal. Calcd. for $C_{29}H_{34}N_2O$ (426.58): C, 81.65; H, 8.03; N, 6.57. Found: C, 80.00; H, 7.95; N, 6.51; Res., 1.09.

For **4bP**: *Anal.* Calcd. for $C_{34}H_{37}N_5O_8$ (655.69): C, 64.11; H, 5.69; N, 10.68. Found: C, 64.19; H, 5.74; N, 10.84.

III. Procedure for Working Under Nitrogen.

The samples of **1** were recrystallized once from ether (A. R.) and dried for 4 hours under vacuum in a drying pistol previously flushed with nitrogen. Care was taken to admit only nitrogen on disassembly of the apparatus.

The amines were fractionally distilled over calcium oxide under nitrogen in a distillation apparatus previously flushed with nitrogen and initial portions were discarded. Both amines were allowed to stand for one week over calcium oxide before distillation.

The *n*-hexane solvent was of analytical reagent grade and was allowed to stand for one week over sodium ribbon before distillation outlined in the previous paragraph.

The reactions were performed in a nitrogen filled glove bag with individual 0.5 g. quantities of **1**, each previously weighed and dried as described above, in 25 ml. Erlenmeyer flasks with ground glass

stoppers using 20 equivalents of the amine.

IV. Preparation of 2-(α-*t*-Butylaminoacetophenonyl)acrylophenone (**2a**).

In 125 ml. of dry ether and 25 ml. of *t*-butylamine was dissolved 2.0 g. of **1** and the solution was allowed to stand at room temperature for 1 hour. The solution was then washed three times with water (500 ml.) and extracted twice with aqueous 3 *N* hydrochloric acid (175 ml.) and immediately neutralized in water under ether with sodium carbonate. The ethereal solution was dried over sodium sulfate. The acid extract (containing most of the material from the original reaction mixture) was nearly pure **2a**. The acid extract was evaporated under reduced pressure to a syrupy light lemon oil which was then placed under vacuum over refluxing ether for three hours, 1.3 g. (65%). A suitable analysis was not obtained.

V. Preparation of α-Acetophenonyl-β-*t*-butylaminoacrylophenone (**3a**).

To 5.0 g. of **1** in 100 ml. of dry ether was added 10 ml. of *t*-butylamine and the solution was allowed to stand overnight. The solution was then filtered and evaporated under reduced pressure to give **3a**, a brown oil (5.4 g.). This oil was then taken up in a small quantity of ether and refrigerated overnight to allow a small amount of **5a** to precipitate, 0.47 g. This oil could not be successfully triturated or precipitated as a solid so a small sample of the oil selectively precipitated from *n*-pentane was placed under vacuum over refluxing ether for 5 hours and analyzed as an oil, 4.3 g. (87%) clear viscous amber.

Anal. Calcd. for $C_{21}H_{23}NO_2$ (321.42): C, 78.47; H, 7.21; N, 4.36. Found: C, 77.30; H, 7.47; N, 4.89.

VI. Reaction of 3-Benzoyl-5-phenylfuran with Amines.

A. Cyclohexylamine. Preparation of α-Acetophenonyl-β-cyclohexylaminoacrylophenone (**3c**).

In 25 ml. of dry ether was dissolved 2.0 g. of 3-benzoyl-5-phenylfuran and 3.0 ml. of cyclohexylamine was added. The reaction mixture was allowed to stand for 4 days and was then washed once with water, twice with a total of 90 ml. of aqueous 1 *N* hydrochloric acid, dried over sodium sulfate and evaporated under reduced pressure. The resulting orange oil was then placed under vacuum for 3 hours over refluxing ether to give 2.4 g. (84%) of viscous orange oil.

Anal. Calcd. for $C_{23}H_{25}O_2N$ (347.44): C, 79.51; H, 7.25; N, 4.03. Found: C, 79.59; H, 7.31; N, 3.92.

Preparation of **5c** by This Method.

In 100 ml. of dry ether was dissolved 3.0 g. of 3-benzoyl-5-phenylfuran and 25 ml. of cyclohexylamine was added. After being allowed to stand at room temperature for 6 days, the reaction mixture was thoroughly washed with water and extracted with aqueous 3 *N* hydrochloric acid. The mother liquor was evaporated to a crude solid which upon recrystallization from ethanol gave a first crop of 1.17 g., m.p. 114-115°. From three successive crops was obtained 1.72 g. (43%).

B. Isopropylamine. Preparation of α-Acetophenonyl-β-isopropylaminoacrylophenone (**3c**).

In 25 ml. of dry ether was dissolved 2.9 g. of 3-benzoyl-5-phenylfuran and 4.5 ml. of isopropylamine was added. After 6 days the reaction mixture was evaporated under reduced pressure and placed under vacuum over refluxing ether for 3 hours to give 2.17 g. (85%) of an orange viscous oil.

Anal. Calcd. for $C_{20}H_{21}O_2N$ (307.44): C, 78.13; H, 6.89; N, 4.58. Found: C, 76.68; H, 6.77; N, 4.87.

Preparation of **5b** by this Method.

In 80 ml. of dry ether was dissolved 1.0 g. of 3-benzoyl-5-phenylfuran and 8 ml. of isopropylamine was added. After 12 days at room temperature the reaction mixture was washed with four 25 ml. portions of aqueous 3 *N* hydrochloric acid, dried over magnesium sulfate and then evaporated under reduced pressure to low volume. The precipitated product was filtered, 0.6 g. (51%) of ivory crystals, m.p. 120-124°.

VII. Preparation of 3-*t*-Butylaminomethyl-2,5-diphenylfuran Hydrochloride.

To a solution of 200 ml. of ether containing 6.0 g. 3-bromomethyl-2,5-diphenylfuran was added 20 ml. *t*-butylamine and the resulting solution refluxed 5.5 hours. The *t*-butylamine hydrobromide salt formed during the reaction was filtered off and the filtrate evaporated under reduced pressure to a yellow-brown oil which solidified. The material was then taken up in ether-ethanol and 10 ml. of aqueous 3 *N* hydrochloric acid was added causing voluminous precipitation of the hydrochloride salt. The mixture was cooled over ice, filtered, washed with ether and dried over a hot plate. A second crop was obtained by acidification of the mother liquor. Combined yield was 5.8 g. (89%) of fine white needles, m.p. 278-281°. Nmr (free base), chloroform-D: multiplet (4 H) at 7.65 ppm (aromatic), multiplet (6 H) at 7.30 ppm (aromatic), singlet (1 H) at 6.83 ppm (olefinic), singlet (2 H) at 3.82 ppm (methylene), broad singlet (1 H) at 1.83 ppm (N-H), singlet (9 H) at 1.22 ppm (*t*-butyl); uv (methanol): 226 mμ (16,600), 309 mμ (26,300).

Anal. Calcd. for $C_{21}H_{24}ONBr$ (386.37): C, 65.28; H, 6.27; N, 3.63; Br, 20.67. Found: C, 65.33: H, 6.34; N, 3.52; Br, 20.44.

VIII. Preparation of *cis*-3-*t*-Butyl-1,2-dibenzoylpropene (**7**).

In 10 ml. of acetic acid was slurried 8.9 g. of 3-*t*-butylaminomethyl-2,5-diphenylfuran and a solution containing 5.6 ml. nitric acid and 17 ml. of glacial acetic acid was added slowly while the mixture cooled in an ice bath. When the solution became clear and amber colored (*ca.* 5 minutes), it was poured into 250 ml. of water and ether was added. The two phase solution was neutralized with sodium carbonate and the ether layer was washed, dried over sodium sulfate and evaporated under reduced pressure to a small volume and the precipitated product was filtered, 4.2 g. The precipitate after washing with ether was recrystallized from ether-petroleum ether; 3.7 g. (46%) long yellow spars, m.p. 118-119.5°. Nmr (chloroform-D): multiplet (4 H) at 7.93 ppm (aromatic), multiplet (7 H) at 7.46 ppm (aromatic and olefinic proton, doublet (2 H) at 3.62 ppm (J = 2 Hz, methylene), singlet (9 H) at 1.13 ppm (*t*-butyl); ir (carbon tetrachloride): 3300 (s), 1665 (l).

Anal. Calcd. for $C_{21}H_{25}NO_2$ (321.42): C, 78.47; H, 7.21; N, 4.36. Found: C, 78.61; H, 7.31; N, 4.32.

IX. Preparation of α-(1-One-acetophenonyl)-β-*t*-butylaminoacrylophenone (**8**).

In 30 ml. of *n*-pentane was slurried 1.6 g. of **7** and 4 ml. of morpholine was added. After one week at room temperature, the reaction mixture was evaporated under reduced pressure, taken up in ether and washed with water. After extraction with aqueous 3 *N* hydrochloric acid, the mother liquor was evaporated under reduced pressure and when dry ether was added to the residue fine white needles of **8** precipitated from the solution; 0.20 g. (19%), m.p. 160-161.5°. Easy crystallization was affected from either chloroform or ether.

Anal. Calcd. for $C_{21}H_{21}O_3N$ (335.39): C, 75.20; H, 6.31; N, 4.18. Found: C, 75.11; H, 6.22; N, 4.26.

X. Preparation of 1-Cyclohexyl-3-benzoyl-4-cyclohexylmethylamino-5-phenylpyrrole (**10**) and its Methiodide Salt (**9**).

In 10 ml. of methyl iodide was dissolved 2.60 g. of **4b** and the solution was refluxed for 20 hours. The mixture was then evaporated under reduced pressure to a dry brown solid. The nmr spectrum in chloroform-D showed a methyl peak at 3.55 ppm (III salt of **10**) and another at 3.53 ppm (**9**); 2:1 ratio, respectively. The solid material was then neutralized with sodium carbonate in water under ether and the ether layer separated, off, dried over sodium sulfate and evaporated under reduced pressure. Upon addition of dry ether to the oil residue, the two compounds separated. A white precipitate of **9** formed and **10** remained in solution. The white powder (**9**) after washing with ethyl acetate weighed 0.30 g., m.p. 117-124°, and the ethereal solution of **10** was evaporated under reduced pressure to a dark orange mossy solid, 2.92 g., m.p. 57-60°. The latter compound is heat sensitive and hygroscopic. The yield was variable depending upon reaction time. The phenylhydrazone of **10**, **10p**, was prepared in the usual manner giving a white crystalline product, m.p. 130-131°.

For **10**, nmr (chloroform-D): multiplet (2 H) at 7.80 ppm (aromatic), multiplet (3 H) at 7.48 ppm (aromatic), singlet (5 H) at 7.37 ppm (aromatic), singlet (1 H) at 7.03 ppm (pyrrole proton), singlet (3 H) at 2.63 ppm (methyl), multiplet (22 H) centered at 1.42 ppm (cyclohexyl).

Anal. for **10p** Calcd. for $C_{39}H_{42}N_4$ (530.73): C, 81.47; H, 7.97; N, 10.56. Found: C, 81.60; H, 8.13; N, 10.27.

For **9** nmr (chloroform-D): multiplet (2 H) at 7.93 ppm (aromatic), singlet (5 H) at 7.65 ppm (aromatic), multiplet (3 H) at 7.55 ppm (aromatic), singlet (1 H) at 7.22 ppm (pyrrole proton), singlet (6 H) at 3.53 ppm (2 methyl groups), multiplet (22 H) centered at 1.50 ppm (cyclohexyl).

Anal. Calcd. for $C_{31}H_{39}ON_2I$ (582.55): C, 63.91; H, 6.75; N, 4.81; I, 21.78. Found: C, 63.94; H, 6.69; N, 4.80; I, 21.76.

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