

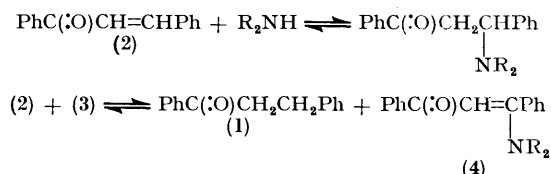
## The Thermal Reaction of Chalcone with Morpholine and Piperidine

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Chalcone (2) reacts at 160 °C with morpholine to give 1,3-diphenylpropan-1-one (1), acetophenone (5), benzomorpholide (6), 2,4,6-triphenylpyridine (7), 1,4-dibenzoyl-2,3-diphenylbutane (8), and di- $\alpha$ -morpholinotoluene (9); 2-( $\alpha$ -morpholinobenzylidene)acetophenone (4) was identified as a reaction intermediate. The reaction of (2) with piperidine proceeds similarly. Evidence is presented which shows that the formation of the various products involves both radical and ionic processes.

SPONTANEOUS redox processes are known to occur in certain organic reactions, examples including the Sommelet reaction<sup>1</sup> and the aromatization of pyridine derivatives.<sup>2</sup> Another example is the reaction of *o*-phenylenediamine with benzaldehyde to give products including 2-phenylbenzimidazole, *N*-benzyl-*o*-phenylenediamine, and 3-benzyl-2,3-dihydro-2-phenylbenzimidazole.<sup>3</sup>

The ready formation of 1,3-diphenylpropan-1-one (1) from the reaction of chalcone (2) with sulphur and morpholine<sup>4</sup> suggested the possibility of obtaining (1) starting from (2) with a secondary amine in the absence of a reactive sulphur species<sup>4,5</sup> through a redox process involving the intermediacy of the  $\beta$ -amino-ketone (3).

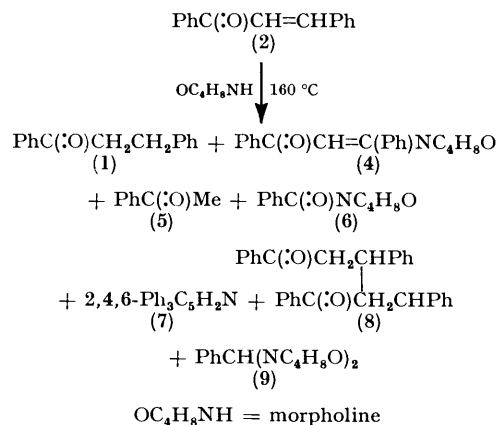


SCHEME 1

### RESULTS

Preliminary experiments showed that when chalcone (2) was heated with morpholine, 1,3-diphenylpropan-1-one (1) was formed in very low yield. When the same reaction was carried out at 160 °C for 20 h, the ketone (1), acetophenone (5), benzomorpholide (6), and small quantities of 2,4,6-triphenylpyridine (7), 1,4-dibenzoyl-2,3-diphenylbutane (8),  $\alpha$ -dimorpholinotoluene (9), and benzaldehyde [derived from the hydrolysis of (9)] were obtained. In some

cases  $\omega$ -( $\alpha$ -morpholinobenzylidene)acetophenone (4) was also identified in the crude reaction mixture.



Piperidine was also used in order to evaluate the effect of amine basicity on the course of the reaction and to establish that the reaction was not specific to morpholine. Some of these reactions were carried out under nitrogen or in the presence of free-radical initiators. The yields of the compounds under various conditions are in Tables 1 and 2.

With the intention of isolating possible reactive intermediates such as the enamino-ketone (4), the reaction time was reduced to 10 h. Under these conditions the enamino-ketone (4) was shown to be present in the reaction mixture of (2) and morpholine (see Experimental section). The enamino-ketone (4) was then allowed to react with morpholine. Compounds (5) and (6) together with small quantities

TABLE 1  
Reaction of chalcone (2) with morpholine or piperidine at 160 °C

Run	Time/h	Products (% yield) <sup>a</sup>						
		(1)	(2)	(5) <sup>b</sup>	(6)	(7)	(8) <sup>c</sup>	Benzaldehyde
1 <sup>d</sup>	20	5.2	77.8	7.6			Trace	1.8
2 <sup>e</sup>	20	4.9	22.4	11.5		4.6	Trace	Trace
3 <sup>f</sup>	20	9.8	21.8	20.5		13.4	Trace	Trace
4 <sup>d</sup>	89	15.3	17.0	23.0	1.0	10.4	1.2	
5 <sup>f</sup>	40	12.6	2.2	31.5		18.6	0.3	
6 <sup>g</sup>	20	6.4	61.8	21.5	1.0	0.5	0.2	3.5
7 <sup>g</sup>	33	10.1	30.2	41.0	2.2	5.1	0.4	
8 <sup>g</sup>	45	11.1	12.0	44.0	1.4	8.6	0.7	
9 <sup>g</sup>	80	13.0	0.9	41.0	2.8	18.7	1.5	
10 <sup>h</sup>	20	5.1	24.7	7.2		17.7	1.4	

<sup>a</sup> The yield of each product was the average of eight runs. Maximum variation in yields was  $\pm 6\%$ . A ratio of compound : amine of 2.4 : 69 (mmol) was used for runs 1–9. <sup>b</sup> In evaluation of the overall yield of (5), it should be remembered that the production of (7) requires 2 equivalents of (5). <sup>c</sup> Yield determined by weighing the compound following collection by filtration. <sup>d</sup> Reaction carried out with morpholine. <sup>e</sup> Reaction carried out with morpholine. The reaction mixture was degassed at  $10^{-4}$  mmHg in several freeze-pump cycles and then sealed. <sup>f</sup> Reaction carried out with piperidine. <sup>g</sup> Reaction carried out with morpholine under nitrogen. <sup>h</sup> Reaction carried out with morpholine in the presence of dibenzoyl peroxide; ratio compound : amine : dibenzoyl peroxide 2.4 : 69 : 0.34 (mmol).

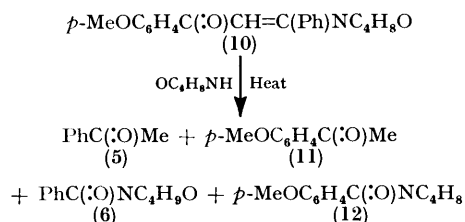
TABLE 2

Reaction of chalcone (2) with morpholine or piperidine at 130 °C

Run	Time/h	Products (% yield) <sup>a</sup>					Benzaldehyde
		(1)	(2)	(5) <sup>b</sup>	(7)	(8) <sup>c</sup>	
1 <sup>d</sup>	20	1.7	65.1	8.3	5.0	Trace	2.0
2 <sup>e</sup>	20	3.6	48.7	6.9	7.6	0.5	
3 <sup>d</sup>	36	3.0	52.0	10.8	7.9	Trace	3.0
4 <sup>e</sup>	36	5.2	38.6	10.6	10.1	1.1	
5 <sup>d</sup>	79	5.3	42.9	12.3	11.7	0.2	4.0
6 <sup>e</sup>	79	6.0	23.0	17.1	14.0	1.4	
7 <sup>f</sup>	30	3.6	23.7	21.2	3.0	0.8	

<sup>a</sup> The yield of each product was the average of eight runs. Maximum variation in yields was  $\pm 6\%$ . A ratio of compound : amine of 2.4 : 69 (mmol) was used; when used, 0.34 mmol of di-*t*-butyl peroxide was added. <sup>b</sup> See footnote *b*, Table 1. <sup>c</sup> See footnote *c*, Table 1. <sup>d</sup> Reaction carried out with piperidine. <sup>e</sup> Reaction carried out with piperidine and di-*t*-butyl peroxide. <sup>f</sup> Reaction carried out with morpholine and di-*t*-butyl peroxide.

of 1,3-diphenylpropan-1-one (1) and *N*-styrylmorpholine were obtained. Similarly, the enamino-ketone (10) reacted with morpholine to give compounds (5), (6), (11), and (12).



It is noteworthy that the reaction of (4) with morpholine under nitrogen led to a larger yield of (5) and (6) (see Table 3).

TABLE 3

Reaction of  $\omega$ -( $\alpha$ -morpholinobenzylidene)acetophenone (4) with morpholine at 160 °C in air or under nitrogen

Time/h	Products (% yield) <sup>a</sup>				
	(1)	(4)	(5)	(6)	<i>N</i> -Styrylmorpholine
Air 20	Trace	17.1	43.0	36.5	Trace
N <sub>2</sub> 20	Trace		85.0	80.5	Trace

<sup>a</sup> The yield of each product was the average of eight runs. Maximum variation in yields was  $\pm 6\%$ . Compound : amine ratio = 2.4 : 69 (mmol).

## DISCUSSION

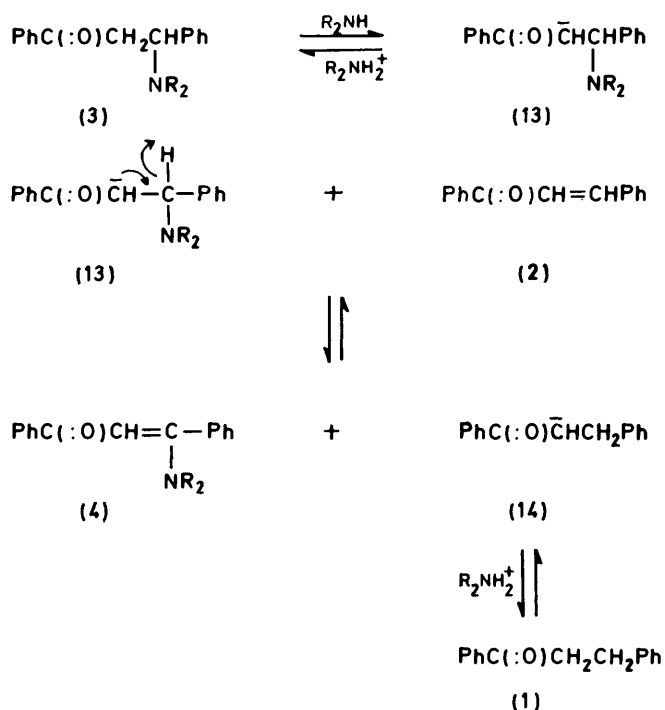
According to reported results,<sup>6</sup> the initial step of the process should involve the addition of the amine to chalcone (2) and formation of the  $\beta$ -amino-ketone (3). Compound (3) could undergo a subsequent redox reaction giving (1), (4), and (8) or undergo fragmentation giving (5), (6), and (9). The formation of (1) and (4) apparently involves the reaction of (3) with chalcone (2) according to Scheme 1.

As the results in Tables 1 and 2 show, the yield of (1) does not change under a nitrogen atmosphere or in the presence of free-radical initiators. This suggests that the reaction leading to (1) proceeds through the ionic intermediates in Scheme 2. According to Scheme 2, the critical step involves hydride transfer from the anion (13) to chalcone.

The yield of acetophenone was found to be significantly higher in the reaction of chalcone (2) with morpholine under nitrogen (see Tables 1 and 2). In addition, the yield of acetophenone was significantly

increased in the presence of a free-radical initiator such as di-*t*-butyl peroxide (Table 2, run 1 vs. run 7) and dibenzoyl peroxide (Table 1, run 1 vs. run 10).

Two mechanisms can be envisaged to explain the formation of acetophenone and benzaldehyde (Scheme



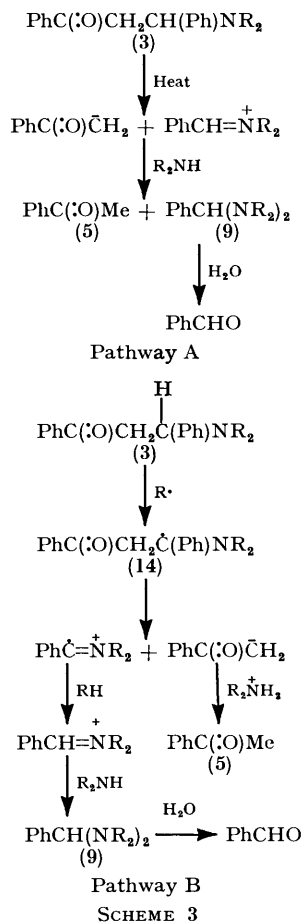
SCHEME 2

3). One (pathway A) involves a retro-aldol reaction of (3) to give two ionic fragments which rapidly react with morpholine to give acetophenone and (9).\*

The results also suggest that the formation of acetophenone may proceed, in part, *via* a free-radical path B. The most reactive position of compound (3) toward hydrogen abstraction is the benzylic carbon atom. Abstraction of the hydrogen atom from this position by

\* The yield of benzaldehyde, obtained by hydrolysis of  $\alpha$ -dimorpholinotoluene (9), was lower than expected. This could be understood from the fact that benzaldehyde is almost completely recovered in reactions with morpholine, or partially recovered from reactions with morpholine and (2) or with morpholine and (5) under nitrogen. However, this point is not relevant to the present study and so these reactions were not further studied.

a free radical would produce the radical (14) from which acetophenone and compound (9) can be derived as shown in Scheme 3.



Although the fragmentation of the radical (14) proposed in pathway B is speculative, this pathway does accommodate the increase in yield of acetophenone and benzaldehyde in the presence of free-radical initiators. Further work is needed to clarify this mechanistic possibility.

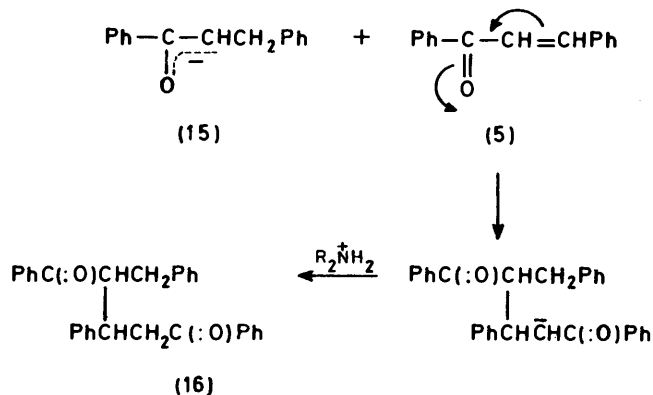
It should also be noted that the yield of compound (7) increased when the yields of (5) and (9) increased.\*

The formation of (7) probably occurs *via* an ionic pathway. A higher yield of this compound was obtained under nitrogen and in the presence of a free-radical initiator (Tables 1 and 2), probably because the fragmentation of the amines needed to obtain compound (7) takes place more readily in the presence of free-radical initiators. It is well known, for example, that amines in the presence of light or di-*t*-butyl peroxide undergo abstraction of the  $\alpha$ -hydrogen atom to produce an imine.<sup>7</sup>

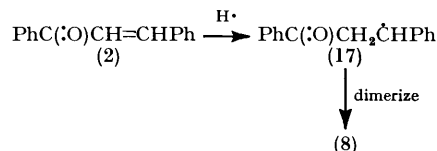
As already mentioned, the formation of (8) is favoured under conditions which are suitable for radical generation. The fact that radical intermediates are involved

\* The yield of benzaldehyde and not of (9) is reported since under the reaction conditions only benzaldehyde is present.

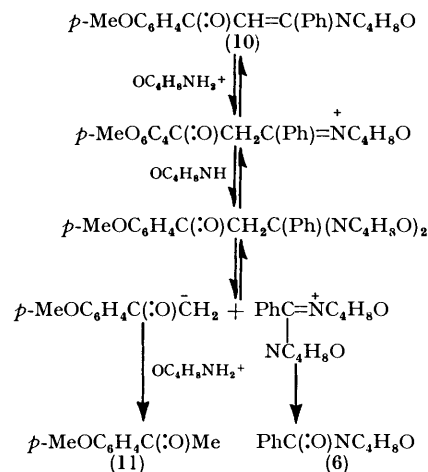
in the formation of (8) is further supported by the symmetry of structure (8) which can be attributed to a free-radical coupling reaction. An ionic mechanism, such as that in Scheme 4, would have been expected to



produce compound (16). The complete absence of compound (16) provides further support for the radical pathway. Scheme 5 outlines a possible pathway for the production of compound (8). 1,3-Diphenylpropan-1-one (1), which might be assumed to be a precursor of (17),



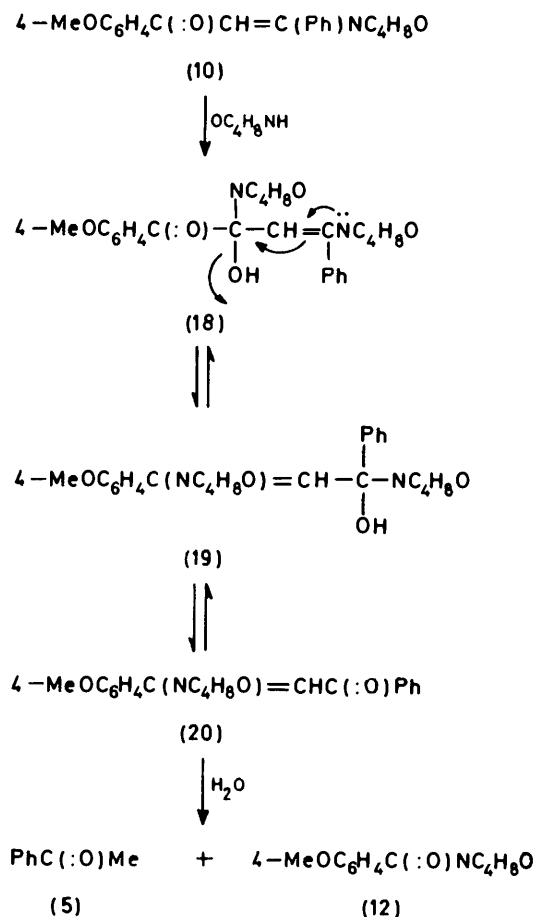
does not give compound (8) under the reaction conditions. 2,4,6-Triphenylpyridine (7) is not obtained in the reaction of (4) with morpholine (see Table 3). The absence of compound (7) tends to suggest that (4) is not a source of the radical (14) which, as suggested in pathway B of Scheme 3, can produce benzaldehyde and acetophenone. We have also shown that compound (4) does



not react with (5) in the presence of amines or ammonia to give the triphenylpyridine (7).

A final point is that the reaction of (10) with morpholine for 20 h at 160 °C afforded a mixture of (5), (6), (11), and (12) (see before). The formation of (11) and (6) can be readily attributed to the hydrolysis of (10). Presumably small quantities of water are present in the system and at the elevated temperatures and long reaction times used, hydrolysis will occur according to Scheme 6.

What is surprising, however, is that compounds (5) and (12) are also found in the reaction mixture. Their formation can be rationalized by assuming that (10) reacts with morpholine across the carbonyl group to give



(18) as a transient intermediate which can undergo subsequent rearrangement to (19), which in turn is converted into the  $\beta$ -enamino-ketone (20). Hydrolysis of compound (20) according to Scheme 7 would readily rationalize the formation of compounds (5) and (12). The reaction of (4) with morpholine at 160 °C under nitrogen led to higher yields of (5) and (6). The significantly lower yields of (5) and (6) in air are perhaps a result of a competing radical process (see Table 3).

#### EXPERIMENTAL

N.m.r. spectra were recorded on a Varian ME 360 spectrometer with tetramethylsilane as internal standard and

deuteriochloroform as solvent. M.p.s were determined on a Reichert apparatus. Mass spectra were obtained with an A.E.I. MS-9 instrument. I.r. spectra were recorded on a Perkin-Elmer 137 spectrophotometer, and u.v. spectra on a Beckman DB-GT spectrophotometer using 95% aqueous ethanol as solvent. T.l.c. analyses were carried out on silica gel F 254 plates; Merck silica gel (0.05–0.2 mm) was used for the chromatographic separations. G.l.c. analyses were performed on a Hewlett-Packard 5758B instrument equipped with a hydrogen flame ionization detector; conditions: 8% silicone gum rubber UCC-982-methylvinyl on Chromosorb W 60–80 mesh (5 ft  $\times$  1/8 in); nitrogen flow rate 40 ml min<sup>-1</sup>; injector temp. 250 °C; detector temp. 290 °C. Naphthalene was used as internal standard. The amines were dried over potassium hydroxide pellets at refluxing temperature for several hours and distilled. The compounds employed, other than (10) were either available commercially or prepared as previously described and purified by standard procedures when necessary.

*G.L.C. Quantitative Analyses.*—Naphthalene was added to the reaction mixture before heating [(5):naphthalene, 2.4:0.46 (mmol)]. The yields given in Tables 1–3 are the average values of at least eight determinations. The maximum variation in yields was  $\pm 6\%$ . Quantitative determination of compound (9) failed because of its decomposition under g.l.c. conditions. The procedure outlined later for the qualitative analyses was then followed.

*4-Methoxy- $\omega$ -( $\alpha$ -morpholinobenzylidene)acetophenone (10).*—Compound (10) was prepared by heating 4-methoxybenzoyl(phenyl)acetylene in excess of dry morpholine until the acetylene derivative disappeared. The amine was removed under reduced pressure and the crude material recrystallized from light petroleum to give the pure *ketone*; m.p. 95–96 °C;  $\delta$ (CDCl<sub>3</sub>) 3.25 (4 H, m), 3.8 (4 H, m), 3.9 (3 H, s), 6 (1 H, s), 6.9 (2 H, m), 7.4 (5 H, m), and 7.9 (2 H, m);  $\nu_{\text{max}}$  (KBr) 1 675 (C=O), 1 110 (C–O–C), and 2 835 cm<sup>-1</sup> (OMe);  $\lambda_{\text{max}}$  (EtOH) 340 ( $\epsilon$  15 000) and 246 nm (6 800) (Found: C, 74.1; H, 6.7; N, 4.0. C<sub>20</sub>H<sub>21</sub>NO<sub>3</sub> requires C, 74.3; H, 6.6; N, 4.3%).

*Procedures.*—(a) The reactions were carried out under the experimental conditions in the Tables using sealed tubes. Runs 6–9 (Table 1) were carried out in a sealed pressure vessel under nitrogen.

The reactions of (2) with morpholine or piperidine led to precipitation of compound (8) after several days at room temperature. The yield of (8) increased markedly when the reactions were carried out in the presence of di-*t*-butyl peroxide or under nitrogen. The precipitation could be accelerated by cooling the mixture after dilution with ethanol. Compound (8) was filtered off and washed repeatedly with water, acetone, and chloroform; m.p. 275 °C (lit.<sup>8</sup> 268–269 °C);  $\lambda_{\text{max}}$  (EtOH) 248 nm [the extinction coefficient was not measured because of the low solubility of (8)];  $\nu_{\text{max}}$  (KBr) 1 680 cm<sup>-1</sup> (C=O) (Found: M<sup>+</sup>, 418. Calc. for C<sub>30</sub>H<sub>26</sub>O<sub>2</sub>: M, 418).

After removal of compound (8) the mixture was diluted with chloroform, repeatedly washed with water, and dried over sodium sulphate. Compounds (1), (2), (5), (6), (7), (9), (11), and (12), and benzaldehyde were obtained by column and thick layer chromatography, and identified by g.l.c. and/or t.l.c., u.v., and i.r. comparison with authentic samples.

The assignment of structure (7), m.p. 135–136 °C (lit.,<sup>9</sup>

135 °C), was supported by its mass spectrum (Found:  $M^+$ , 307. Calc. for  $C_{23}H_{17}N$ :  $M$ , 307).

(b) When the mixture of chalcone (2) and morpholine was heated at 160 °C for 10 h, the enamino-ketone (4) was obtained in addition to the foregoing components. Compound (2) was identified by g.l.c., t.l.c., u.v., and i.r. comparison with an authentic sample.

*Reactions of 1,3-Diphenylpropan-1-one (1) and Morpholine.*

—(a) *With di-*t*-butyl peroxide.* A mixture of 1,3-diphenylpropan-1-one (1) (504.4 mg, 2.4 mmol), morpholine (69 mmol), di-*t*-butyl peroxide (49.64 mg, 0.34 mmol), and naphthalene \* (58.88 mg, 0.46 mmol) was heated in a sealed tube at 130 °C for 60 h. Compound (8) was not detected.

(b) *With dibenzoyl peroxide.* A mixture of 1,3-diphenylpropan-1-one (4) (504.4 mg, 2.4 mmol), morpholine (69 mmol), dibenzoyl peroxide (82.35 mg, 0.34 mmol), and naphthalene \* (58.88 mg, 0.46 mmol) was heated in a sealed tube at 160 °C for 60 h. As in (a), compound (8) was not detected (5).

*Reaction of  $\omega$ -( $\alpha$ -Morpholinobenzylidene)acetophenone (4) with Acetophenone (5) and Morpholine.*— $\omega$ -( $\alpha$ -Morpholinobenzylidene)acetophenone (4) (251.6 mg 1.2 mmol), acetophenone (5) (144 mg, 1.2 mmol), morpholine (34.5 mmol), and naphthalene \* (44.8 mg, 0.35 mmol) were heated in a sealed pressure vessel under nitrogen at 160 °C for 48 h. 2,4,6-Triphenylpyridine (7) was not detected.

*Reactions of Benzaldehyde.*—(a) *With morpholine.* Benzaldehyde (254.4 mg, 2.4 mmol), morpholine (69 mmol), and naphthalene \* (58.88 mg, 0.46 mmol) were heated in a sealed pressure vessel under nitrogen at 160 °C for 20 h. After hydrolysis g.l.c. showed the presence of 90% of the starting benzaldehyde.

(b) *With morpholine and acetophenone (5).* A mixture of benzaldehyde (254.4 mg, 2.4 mmol), morpholine (69 mmol),

\* Internal g.l.c. standard.

acetophenone (5) (288 mg, 2.4 mmol), and naphthalene \* (58.88 mg, 0.46 mmol) in a sealed pressure vessel under nitrogen was heated at 160 °C for 20 h. After hydrolysis the following compounds were identified and their amounts estimated by g.l.c. analysis: acetophenone (5) (32%), 2,4,6-triphenylpyridine (7) (40.7%), 1,3-diphenylpropan-1-one (1) (4.7%), chalcone (2) (trace), and benzaldehyde (3%).

(c) *With morpholine and chalcone (2).* Benzaldehyde (254.4 mg, 2.4 mmol), morpholine (69 mmol), chalcone (499.2 mg, 2.4 mmol), and naphthalene \* (58.88 mg, 0.46 mmol) were heated in a sealed pressure vessel under nitrogen at 160 °C for 20 h. After hydrolysis the following compounds were identified and their amounts estimated by g.l.c.: 1,3-diphenylpropan-1-one (1) (6.2%), chalcone (2) (8.57%), acetophenone (5) (15%), 2,4,6-triphenylpyridine (7) (26.4%), and benzaldehyde (16%).

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